30
#11

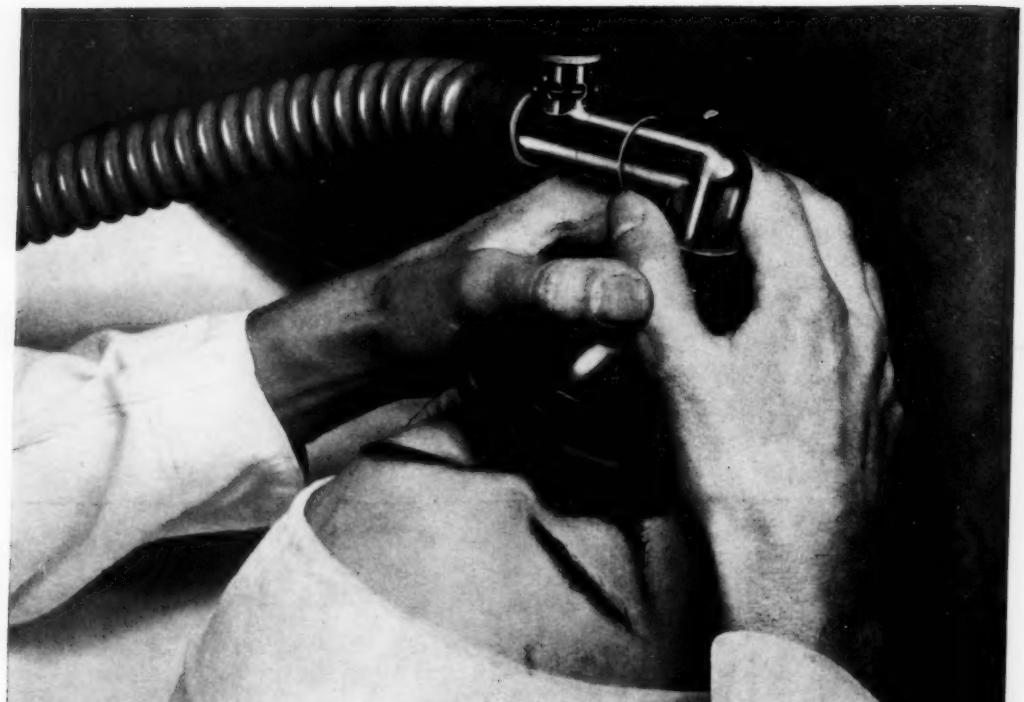
Clendening
Medical Library
DEC 30 1958
University of Kansas
Medical Center

British Journal of Anaesthesia

JOINT EDITORS:
E. FALKNER HILL T. CECIL GRAY
Editor of Postgraduate Educational Numbers R. P. HARBORD

Volume XXX **No. 11** **November 1958**

JOHN SHERRATT & SON : *Publishers*
ALTRINCHAM ENGLAND



'Fluothane', the new inhalation anaesthetic, has 8 important advantages

The important advantages of 'Fluothane' over other inhalation anaesthetics have been demonstrated in two ways: first by experiment; then in clinical trials covering many thousands of cases, involving patients of all ages undergoing all types of surgical operation.

The special characteristics of 'Fluothane' merit the attention of every practising anaesthetist. They show that this new drug is a most valuable contribution to the greater efficiency and greater safety of modern anaesthesia.

1. *Non-explosive and non-inflammable when mixed in any proportion with oxygen.*
2. *Therapeutic ratio twice that of ether.*
3. *Four times as potent as ether and twice as potent as chloroform.*
4. *Easily administered, with pleasant and rapid induction.*
5. *Suppression of salivary, bronchial and gastric secretions.*
6. *Bloodless field, facilitating surgery.*
7. *Absence of shock syndrome.*
8. *Rapid and comparatively uneventful recovery.*

Fluothane TRADE MARK An I.C.I. discovery

IMPERIAL CHEMICAL INDUSTRIES LIMITED Pharmaceuticals Division Wilmslow Cheshire
Ph.804

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOL. XXX, No. 11 NOVEMBER 1958

EDITORIAL

WE publish in this number the first of Professor J. Y. Simpson's pamphlets on chloroform entitled "New Anaesthetic Agent as a Substitute for Sulphuric Ether in Surgery and Midwifery". The date at the end of the article reads as follows, "Edinburgh, 15th November, 1847" and the concluding paragraph "I have up to this date exhibited the Chloroform to about fifty individuals. In not a single instance has the slightest bad result of any kind whatever occurred from its employment". Writing on 15th November one hundred and eleven years later it has unfortunately to be admitted that some bad results have followed the exhibition of chloroform during this period. When, however, we set these bad results against the good, they sink into insignificance. A moment's thought will call to mind the immense relief from pain which has followed the use of chloroform and also the innumerable life-saving operations that have been performed by means of its help. Insignificant though the bad results of chloroform may be when compared with the benefits that its use has conferred on humanity, they have been a spur to stimulate anaesthetists, surgeons, physiologists and chemists to find other means, drugs or methods, of relieving pain and producing relaxation of muscles that have not the drawbacks of chloroform. So successful have we been that chloroform is very little used today, perhaps too little. Owing to its great power, easy portability and comparatively high boiling point, it would seem that there are circumstances in which its use would be indicated, but its sphere of usefulness has been severely restricted. Professor Simpson gives its advantages compared with ether as those of power, portability and pleasantness. Today, however, chloroform has other rivals; curare will give muscular relaxation, but as it is not an anaesthetic it needs assistance; spinal anaesthesia gives anaesthesia and relaxation, and halothane, the very latest product that the chemists have given us, has made a very promising start and would be preferred by most anaesthetists to chloroform. Whereas Simpson was able to state that he had given chloroform to fifty individuals without any bad result whatever, the modern anaesthetist might claim that he had given some hundreds of cases halothane with a like happy outcome. We expect to publish other extracts from Simpson's writings in our forthcoming numbers.

"The Treatment of Barbiturate Poisoning" by R. P. Wise calls attention to the very rapid increase in the number of deaths due to poisoning by the barbiturates. He concludes his paper with the following: "In large centres of population the setting up of special units for treating cases of barbiturate poisoning, as has been done in Scandinavia would help in reducing the mortality to the unavoidable minimum". We should have thought that the staff and equipment of any of our hospitals "in large centres of population" were competent to deal such emergencies and the establishment of a special department for dealing with cases of barbiturate poisoning was not of high priority. The article does raise other questions, if not of high priority certainly of profound importance. How far are we, the medical profession, responsible? The late Sir William Willcox condemned the giving of the barbiturates altogether. Are we right in ignoring his advice? Is there any reason to suppose that their regular use is conducive to cerebral deterioration? When your patient complains that he cannot sleep, the easy way out is to prescribe a barbiturate. Is it the right way out? These are questions the answers to which are of extreme importance, but until we get them there is a good deal to be said on both sides.

Brit. J. Anaesth. (1958), **30**, 506

THE SIMULTANEOUS ADMINISTRATION OF THIOPENTONE PLUS BEMEGRIDE OR OTHER DERIVATIVES OF GLUTARIC ACID TO DOGS

BY

G. A. BENTLEY AND S. SAVIDGE

Nicholas Institute for Medical and Veterinary Research, Victoria, Australia

THE simultaneous administration of a therapeutically valuable drug together with another drug having antagonistic actions might appear to be a futile procedure. However, there could be certain combinations in which the antagonizing drug specifically reduced or abolished some of the undesirable side effects of the therapeutic compound, without materially affecting the properties for which this drug was given.

Gershon and Shaw (1957) have investigated combinations of bemegride (Megimide) plus phenobarbitone or amylobarbitone given orally to human patients. They were able to show that the dose response curves of such mixtures were bell-shaped. At low doses, the sedation produced was indistinguishable from that produced by the same dose of barbiturate alone; as the dosage of the barbiturate-bemegride mixture was increased, the depth and duration of narcosis at first increased, and then, at high doses, decreased, until, at the highest dosage, some patients were observed who did not sleep at all. It would appear from these results that the dose-response curve of bemegride is steeper than that of the barbiturates, and as the dosage of the mixture is increased, the action of the bemegride "overtakes" that of the barbiturates. The main object of Gershon and Shaw's work was to produce a barbiturate mixture, overdosage with which would not cause serious intoxication.

It therefore seemed important to test whether such a protective action of bemegride could be shown against intravenously administered thiopentone. If it could also be proved that no reduction of the anaesthetic potency of the thiopentone was caused by the bemegride, the therapeutic ratio of the thiopentone would be improved. Two related compounds were also tested. These were N.P.42 (the sodium salt of $\beta\beta$-methyl-ethyl glutaramic acid) and N.P.275 (the sodium salt of $\beta\beta$-methyl-isopropylglutarimide). Accordingly, experiments were performed to determine the following points:

(i) Do these analeptics affect the anaesthetic potency of thiopentone when the two compounds are given simultaneously?

(ii) For a given dose of thiopentone, does the addition of bemegride alter the duration of anaesthesia?

(iii) Do bemegride or the related analeptics alter the dose of thiopentone that will cause permanent cessation of respiration?

(iv) Is the oxygen content of venous blood following a given dose of thiopentone altered by a simultaneous dose of bemegride?

METHODS

Ampoules of Pentothal (Abbott) brand of thiopentone were used throughout. Bemegride (Megimide) was available as the sodium salt, a white powder soluble in water to 5 per cent, giving a strongly alkaline solution. N.P.42 has been shown to have weak barbiturate antagonist action, and was included chiefly because it was very soluble in water, and therefore high levels could be attained. N.P.275 has about 5 times the activity of bemegride as a barbiturate antagonist. It was available as a white powder, soluble in water to about 1 per cent.

The doses of thiopentone were diluted individually for each dog in such a manner that each millilitre of the resulting solution contained 5 mg/kg of thiopentone for a given dog. For instance, for a dog weighing 10 kg, 1 gram of thiopentone was diluted to 20 ml, giving a solution containing 50 mg/ml. By this means,

identical volumes given to the series of dogs gave identical doses in mg/kg. When bemegride or the other derivatives of glutaric acid were used, the appropriate quantity of the dry sodium salt was added to the thiopentone in the ampoule, and this was then diluted appropriately.

(1) Adult crossbred dogs of both sexes were used. They were weighed immediately before use. For experiments on the effect of the analeptics on the anaesthetic potency of thiopentone, a standard procedure of injection was maintained throughout all experiments. A volume of 3 ml of the anaesthetic solution was injected rapidly into the median cephalic vein. This invariably caused the dog to collapse in a few seconds. Exactly 1 minute later a further 1 ml (5 mg/kg) was administered, during a period of exactly 20 seconds. After a further 40 seconds, the next millilitre of solution was given and this procedure of injecting at exactly one-minute intervals was continued until the desired dose was reached.

(2) In the experiments concerned with sleeping times, and a few of the earlier determinations of doses producing apnoea, a minor variation in this procedure was used. Four ml were injected initially, and the subsequent doses were given at 2-minute intervals.

In all cases, the animals served as their own controls, receiving at intervals of not less than one week, thiopentone or thiopentone plus the antagonist drug. To eliminate effects of tolerance, etc., one half of the animals received the thiopentone first, and the other half was given the mixture first.

It is very difficult to assess exactly the depth of anaesthesia produced by the thiopentone. In two cases, it was attempted to correlate changes in the encephalographs of dogs with changes in the plane of anaesthesia, particularly with the onset of "full surgical anaesthesia". However, it was found that such encephalographic changes were too gradual to be of any value. Furthermore, changes in pupil size or in the position of the nictitating membrane, were found to be of no value in assessing the onset of surgical anaesthesia. The corneal reflex was often found to persist to a very deep plane of anaesthesia. The paw withdrawal reflex on the other hand is more satisfactory. In the present experiments, the reflex was scored as "present" when a firm pinch to the interdigital web of the hind foot caused retraction of the whole leg, as "just present" (or $\pm$) when only a slight movement of the foot resulted, and as "absent" when it became impossible to elicit any movement at all.

After the animals had been anaesthetized, they were placed in a warm room, and observed continuously. Respiration rate was noted after 3 to 5 minutes, and again at 10 to 20 minutes, and the dogs were patted firmly every 10 minutes until they could walk. The paw withdrawal reflex was also tested every 10 minutes until the dog reacted vigorously to the pinch.

(3) For determining the dose of thiopentone or thiopentone plus bemegride which produced apnoea, the drugs were injected at one-minute intervals as described above (section 1) until the dogs ceased breathing for one minute. No attempt was made to resuscitate them during this period, and if they did not recover spontaneously, they were considered "dead" for the purposes of the experiment. At the conclusion of the one minute of apnoea, artificial respiration was commenced, and a dose of 10–20 mg/kg of sodium bemegride was given intravenously. In most cases, this produced recovery of spontaneous respiration within 3 minutes, and the dogs were placed in a warm room until they were fully recovered. In this manner, they were available for "cross-over" experiments.

(4) Estimation of venous blood oxygen saturation was carried out spectrophotometrically using a Waters type cuvette (Nahas, 1950). Several 2-ml syringes were taken, and in each was placed a thin annulus of soft iron, which, when agitated by an external magnet, rapidly mixed the contents of the syringe. The dead space of the syringe was filled with heparin and saturated saponin solutions. Two minims of each of these solutions were injected from tuberculin syringes into the 2-ml syringes. Care was taken to exclude all air bubbles.

Following the method of Nahas, a calibration curve of blood oxygen was drawn up. Venous blood was taken from 4 dogs in the manner described above. The optical densities at 505 $m\mu$ and 605 $m\mu$ of these samples when completely reduced and fully oxygenated was determined, and a curve was constructed from these figures.

A control blood sample was taken from the

median cephalic vein of each dog. The blood was drawn into the syringe to the 2-ml mark, mixed rapidly and placed in the cuvette within 3–5 minutes of withdrawal. The optical density was determined after a further 5–7 minutes.

Thiopentone, 40 mg/kg, with or without bemegride, 10 mg/kg, was then injected using the procedure described in section (1). Further 2-ml samples of blood were taken from each dog 2, 5, and 10 minutes after the barbiturate.

It is known that in both the sheep (Turner and Hodgetts, 1958) and the dog (Hahn et al., 1943) anaesthesia can cause relaxation of the spleen, and a consequent drop in the amount of circulating haemoglobin. To allow for this, haemoglobin estimations were made on every sample of blood taken. This was done colorimetrically using a Hellige haemoscope. Between 1 and 2 weeks later, the dogs were "crossed over", those that had received thiopentone alone receiving thiopentone plus bemegride and vice versa.

The oxygen capacity of the blood from the dogs was calculated from its haemoglobin content and percentage saturation, assuming that 1 gram fully oxygenated haemoglobin contains 1.34 volumes of oxygen.

RESULTS

(1) *The effect of bemegride, N.P.42, and N.P.275 on the dose of thiopentone which causes disappearance of the paw withdrawal reflex.*

Table I shows the results of these experiments. None of the drugs tested had any significant effect on the minimum anaesthetic dose of thiopentone. It can also be seen that there were sometimes small variations in this minimum anaesthetic dose when the same dog was tested on different occasions, whether antagonists were used or not.

(2) *The effect of bemegride on the sleeping times of dogs given thiopentone.*

The results are set out in tables II and III.

TABLE I

Dose of thiopentone to just abolish paw withdrawal reflex.

Dog. No.	Sex	Thiopentone alone	Thiopentone + Bem. 5:1	Thiopentone + Bem. 4:1	Thiopentone + Bem. 3:1	Thiopentone + NP.42 1:1	Thiopentone + NP.275 20:1
1	F	25, 30	—	—	30	—	—
2	F	30	—	35	—	—	—
3	F	30	—	—	30	—	30
4	M	25, 30	—	20, 25	25	—	—
5	M	20	—	25	—	—	—
6	F	30, 30, 25, 25, 25, 30	—	30, 25	30	—	—
7	F	30	—	25	—	—	—
8	M	30	—	—	—	—	30
9	M	25, 30, 30	—	30, 25	—	—	—
10	M	30, 30, 30	—	25, 25	—	—	30
11	M	20, 30	—	30, 25	—	—	25
12	M	25	—	30	—	—	—
13	M	25	—	25	—	—	—
14	F	20, 30, 35	—	35	—	30	30
15	F	30, 35	—	35	—	—	—
16	M	25, 25, 25	—	30, 25	—	—	—
17	F	25	—	30	—	25	—
18	F	25, 30, 30	—	30, 30	—	25	—
19	F	30	—	—	—	30	—
20	F	30	—	30, 30	—	25	—
21	F	30, 30, 30	30	30, 30	—	—	—
22	F	25, 30	30	30, 30, 25	—	—	—
23	M	30	—	30	—	—	—
24	M	30	—	30	—	—	—
25	M	30	30	—	—	—	—
26	M	30	25	—	—	—	—
27	M	22.5	25	—	—	—	—
28	M	25	25	—	—	—	—
29	M	23	23	—	—	—	—
30	M	30	30	—	—	—	—

TABLE II

Thiopentone 30 mg/kg, sodium bemegride 6 mg/kg (5:1) in dogs. Each dog acts as its own control.

Dog No.	Dose producing surgical anaesthesia (mg/kg)		Resp/min at 3–5 min	Resp/min at 10–20 min	Return of paw W/D reflex (min)	Commence to stretch (min)	Return of neck tone (min)	Head lifted (min)	Sitting (min)	Crawling (min)	Walking (min)
145 (M)	Control	30	12	12	27±, 52+	30	100	110	120	120	160
14.1 kg	Test	30	14	10	21±, 41+	21	41	51	51	69	69
74 (M)	Control	30	12	14	24±, 44+	34	51	64	74	79	81
20.5 kg	Test	25	12	22	10±, 14+	30	30	31	32	42	45
176 (M)	Control	22.5	10	14	50	40	65	65	67	72	118
13.6 kg	Test	25	8	10	23±, 33+	23	51	51	56	56	63
177 (M)	Control	25	28	21	21±, 50+	30	135	139	141	151	165
13.2 kg	Test	25	26	22	23+	27	73	107	110	111	118
175 (M)*	Control	23	apnoeic 2–3		90	55	>110	115	140	>150	160
12.7 kg	Test	23	28	34	42±, 52+	32	72	87	100	117	119
186 (M)	Control	30	12	16	25±, 70+	55	80	90	100	102	110
14.8 kg	Test	30	10	14	20±, 40+	30	55	65	75	85	95
140 (F)	Control	30	40	40	<25	<25	45	55	>65	75	80
11.4 kg	Test	30	44	32	14±, 24+	24	24	34	43	45	52
141 (F)	Control	30	15	12	30	30	90	95	96	104	105
9.1 kg	Test	30	26	18	20	—	35	50	60	100	105

* Received 35 mg/kg thiopentone + 7 mg/kg sodium bemegride.

TABLE III

Thiopentone 30 mg/kg, sodium bemegride 7.5 mg/kg (4:1) in dogs. Each dog acts as its own control.

Dog No.	Dose producing surgical anaesthesia (mg/kg)		Resp./min at 3–5 min	Resp./min at 10–20 min	Return of paw W/D reflex (min)	Commence to stretch (min)	Return of neck tone (min)	Head lifted (min)	Sitting (min)	Crawling (min)	Walking (min)
140 (F)	Control	25	26	29	40±, 50+	40	70	88	90	90	92
13.2 kg	Test	25	24	24	33±, 43+	33	43	59	65	68	73
141 (F)	Control	30	18	18	25±, 35+	55	90	104	106	—	120
10.2 kg	Test	30	24	14	42±, 49+	42	62	96	97	—	111
187 (F)	Control	25	20	14	54±, 62+	58	67	70	78	87	104
16.1 kg	Test	25	12	12	25±, 35+	25	61	66	71	77	82
161 (F)	Control	30	16	14	45±, 55+	55	85	91	114	115	117
12.5 kg	Test	30	9	16	27±, 37+	48	48	60	71	75	80
163 (F)	Control	30	24	12	51±, 73+	51	73	78	90	—	101
11.8 kg	Test	30	28	15	33±, 53+	53	73	77	79	84	89

Several points may be emphasized. It may be seen that the anaesthetic potency of the thiopentone is not affected by either concentration of bemegride although the duration of surgical anaesthesia (i.e. to the return of paw withdrawal reflex) was reduced in every case except one (dog no. 2, table III). It can also be seen that bemegride in every case caused a reduction in the time to return of the ability to walk.

(3) *The effect of bemegride on the acute toxicity of thiopentone.*

In every case, the apnoea-producing dose of thiopentone when combined with bemegride was higher than that of thiopentone alone.

This increased margin of safety varied between 10 and 20 mg/kg. There seems to be no advantage, as far as considerations of toxicity are concerned, in increasing the amount of bemegride above a ratio of 1:4. The related glutaramide, N.P.275, also lessened toxicity. However, it was noted in several cases that a delayed respiratory failure occurred, 5 to 15 minutes after normal respiration had been re-established. This could usually be reversed by further doses of bemegride but 2 dogs died in spite of this treatment. They had first ceased breathing after having 60–65 and 50–50 mg/kg thiopentone plus 1/20 of this dose of N.P.275. As these were not "crossed over" they are not included in table IV. N.P.42 also reduced the toxicity of thiopentone, but the effect was less reliable than with bemegride.

(4) *Blood oxygen determinations.*

None of the 6 dogs showed any respiratory embarrassment after receiving 40 mg/kg thiopentone with 10 mg/kg bemegride. On the other hand, two of these dogs had temporary apnoea after receiving this dose of thiopentone alone, and a third dog died, in spite of being artificially respired (dog 3, table V).

The results of the determinations are set out in table V and are illustrated graphically (fig. 1). The greatest effects are to be seen at the 2- and 5-minutes estimations. The blood of the dogs receiving bemegride plus thiopentone had a greater percentage oxygen-saturation of haemoglobin, and a higher oxygen content than when they received the same dose of thiopentone alone. In 4 cases, this difference in oxygen content lay between 150 and 230 per cent of the control values. In the period between 5 and 10 minutes after the anaesthetic, the control values tended to approach those with bemegride.

DISCUSSION

Various authors have shown that other analeptics can lessen respiratory depression resulting from narcotics. For instance, Booker and his coworkers (1950) have shown that pentamethylenetetrazole will protect dogs from otherwise toxic doses of thiopentone if given immediately after the anaesthetic. However, very large doses of the analeptic were necessary. Anderson and Teague (1956) showed, also in dogs, that both pentamethylenetetrazole and picrotoxin improved the arterial blood oxygen saturation of animals deeply depressed with dial-urethane. However, in most cases, doses necessary to produce this improvement also caused twitchings or even frank convulsions.

TABLE IV

The effect of bemegride, N.P.42 and N.P.275 on the dose of thiopentone producing apnoea in dogs.

Dog	Sex	Thiopentone alone	Thiopentone + bemegride			Thiopentone + N.P.42	Thiopentone + N.P.275
			4:1	3:1	2:1	1:1	20:1
1	F	40–45	50–55	60–65	—	—	—
2	M	35–40	50–55	—	—	—	—
3	M	45–50	>65	55–60	>68	—	—
4	M	35–40	45–50	—	—	—	—
5	F	35–40	—	50–55	—	—	40–45
6	M	55–60	75–80	—	—	—	>70
7	F	35–40	45–50	45–50	—	—	45–50
8	F	50–55	—	—	—	55–60	—
9	F	55–60	—	—	—	55–60	—
10	F	45–50	—	—	—	60–65	—
11	F	45–50	—	—	—	55–60	—

TABLE V
Blood oxygen determinations

Dog No.	Sex	Medication	Time	Hb conc. (g/100 ml)	% saturation	Vol. oxygen
1	F	thiopentone 40 mg/kg	before	17.1	90	20.6
			2 min after	17.6	33	7.6
			5 min after	16.9	60	13.6
			10 min after	15.4	62	12.8
		thiopentone 40 mg/kg + bem. 10 mg/kg	before	16.5	83	18.4
			2 min after	17.0	38	8.7
			5 min after	15.3	43.5	8.9
			10 min after	14.9	79	15.8
2	M	thiopentone 40 mg/kg	before	22.0	81	23.9
			2 min after	20.8	35.5	9.9
			5 min after	18.1	58.5	14.2
			10 min after	18.1	69.5	16.9
		thiopentone 40 mg/kg + bem. 10 mg/kg	before	20.7	77	21.4
			2 min after	18.6	55	13.7
			5 min after	18.2	63	15.4
			10 min after	17.1	73	16.7
3	M	thiopentone 40 mg/kg	before	13.4	65	11.7
			2 min after	13.4	23.5	4.2
			5 min after	13.0	20	3.5
			10 min after	12.5	16	2.7
		thiopentone 40 mg/kg + bem. 10 mg/kg	before	15.4	92	19
			2 min after	14.2	31.5	6
			5 min after	13.9	63.5	11.8
			10 min after	13.2	74.5	13.2
4	M	thiopentone 40 mg/kg	before	18.4	79	19.5
			2 min after	17.8	29	6.9
			5 min after	16.6	58	12.9
			10 min after	15.6	59	12.3
		thiopentone 40 mg/kg + bem. 10 mg/kg	before	16.9	92	20.8
			3 min after	15.1	73	14.8
			10 min after	14.9	81	16.2
5	M	thiopentone 40 mg/kg	before	19.9	72	19.2
			3 min after	22	8.5	2.5
			10 min after	17.1	65	14.9
		thiopentone 40 mg/kg + bem. 10 mg/kg	before	18.4	70.5	17.3
			2 min after	15.9	23.5	5.0
			5 min after	15.3	59	12.1
			10 min after	13.6	64	11.7
6	F	thiopentone 40 mg/kg	before	20.5	74	20.3
			2 min after	21.5	32.5	9.4
			5 min after	20.1	43	11.6
			10 min after	18.7	50	12.5
		thiopentone 40 mg/kg + bem. 10 mg/kg	before	21	80.5	22.7
			2 min after	19.4	69	17.4
			5 min after	17.4	72	16.8
			10 min after	18.3	75	18.4

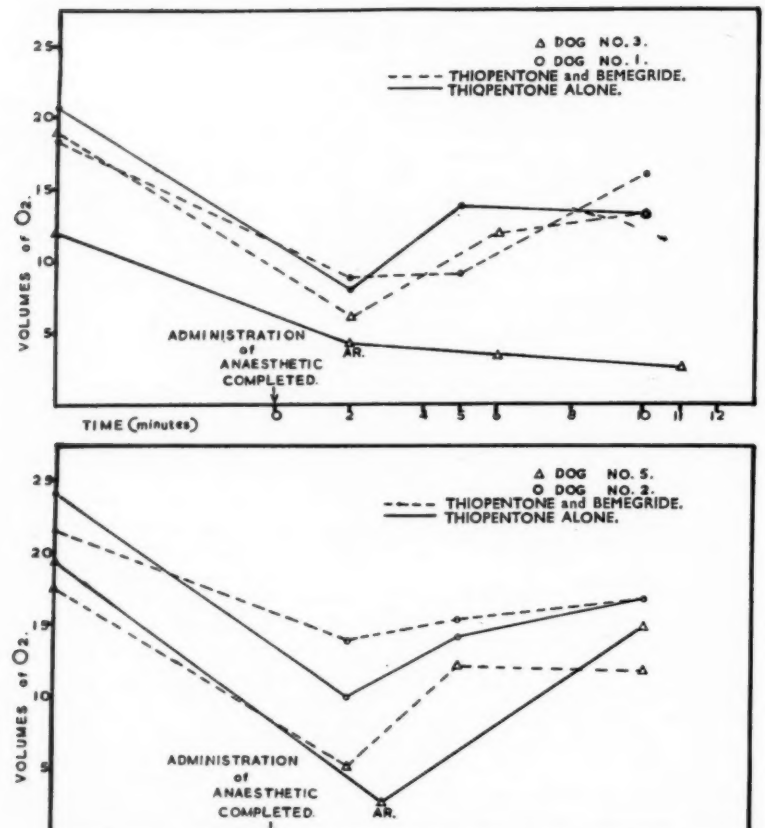


FIG. 1

Graphs comparing the effects of thiopentone alone and in the presence of bemegride (1:4) on the oxygen content of dogs' blood.
A.R.=Artificial respiration needed.

The results of the present paper show that bemegride also had this beneficial effect against thiopentone depression. However, it produced this effect in much smaller doses than were needed for pentamethylenetetrazole, and at no time were there any suggestions of excitation. In fact, even with a mixture containing as much as one part of bemegride to three parts of thiopentone, the narcotic potency of the thiopentone was not in any way reduced, and no signs of excitement were seen, even during induction.

The results in the section on blood oxygen levels require some further comment. It will be noted that the control haemoglobin levels in a given dog may vary within wide limits when estimated on different occasions. Since in 5 of the 6 cases, the second estimation was lower than the first, it seems possible that some degree of anaemia resulted from the anaesthesia. Another factor likely to contribute to this variation in haemoglobin level is the degree of excitement of the animal. Various workers have shown marked variations in circulating erythrocytes of horses (Irvine, 1957), sheep (Turner and Hodgetts, 1958), and dogs (Hahn et al., 1942) following such stresses as exercise, fear, or adrenaline injections. These findings seem to provide an adequate explanation for the variations in haemoglobin levels found in the present investigation. The drop in haemoglobin levels following anaesthesia (table V) is in agreement with the findings of Hahn et al. (1943) who showed that pentobarbitone but not ether caused sequestration in the spleen of up to 30 per cent of the circulating erythrocytes. Bemegride apparently does not affect this drop in circulating erythrocytes.

Tests have also been done on the toxicity of thiopentone in the presence of N.P.42 and N.P.275. The weak action of N.P.42 was not surprising, as other work has shown that even in high doses, its ability to shorten the sleeping time of mice dosed with pentobarbitone was slight (Macfarlane, A. W., personal communication). On the other hand, the results with N.P.275 were rather disappointing. This compound produces all the effects of bemegride at 1/5th to 1/10th of the dose (Macfarlane, A. W., personal communication). Although it raised the toxic dose of thiopentone, its action appeared to be very transient, and a secondary depression occurred.

THE PRACTICAL USE OF THE MIXTURE

In these laboratories, on many occasions, experimental animals, both cats and dogs, have been anaesthetized with the mixture of thiopentone plus bemegride. Manoeuvres such as insertion of carotid and tracheal cannulae, laparotomy, etc., have been performed. The occasional addition of further doses of 5 mg/kg thiopentone plus 1.25 mg/kg bemegride as needed has enabled surgical anaesthesia to be prolonged for 5 hours or more, without any signs of respiratory or circulatory failure.

The mixture has also been successfully used in surgery on human cases (Capponi, R., personal communication). However, in the human, a lower proportion of bemegride is required than for the dog. More than one hundred cases have been anaesthetized using a solution containing 500 mg thiopentone plus 50 mg bemegride in a volume of 10 ml. Respiratory depression was less than with corresponding doses of thiopentone alone, recovery was quicker, and no cases of laryngeal spasm were seen.

CONCLUSIONS

The addition of bemegride to thiopentone, produces an intravenous anaesthetic with the following advantages over thiopentone alone:

(*a*) reduced toxicity;

(*b*) lessened respiratory depression;

(*c*) shorter duration of action.

Furthermore, addition of bemegride up to a ratio of 1:3 does not affect the anaesthetic potency of the thiopentone. Hence an improvement of the therapeutic ratio of thiopentone has been achieved. Frequent laboratory use of the mixture has shown that it is a very satisfactory and safe anaesthetic for surgery lasting from a few minutes to several hours, according to the dose used.

Two other related derivatives of glutaric acid, N.P.42 and N.P.275, also reduce the toxicity of thiopentone, but are less effective.

REFERENCES

Anderson, W. R., and Teague, R.S. (1956). The effect of analeptics on arterial blood gases of dogs during barbiturate anaesthesia. *J. Pharmacol. exp. Ther.*, **118**, 369.

Booker, W. M., Molano, P. A., French, D. M., and Rhodes, C. (1950). Re-evaluation of effectiveness of pentamethylenetetrazol (Metrazol) as analeptic agent during thiopental depression. *J. Pharmacol. exp. Ther.*, **98**, 207.

Gershon, S., and Shaw, F. H. (1957). Effects of bemegride on barbiturate overdosage in humans. *Brit. med. J.*, **2**, 1509.

Hahn, P. F., Bale, W. F., and Bonner, J. F. (1942). Mechanisms of effect of Epinephrine on venous hematocrit value of normal unanesthetized dog. *Amer. J. Physiol.*, **137**, 717.

Hahn, P. F., Bale, W. F., and Bonner, J. F. (1943). Removal of red cells from active circulation by sodium pentobarbital. *Amer. J. Physiol.*, **138**, 415.

Irvine, C. H. G. (1957). The blood picture in the horse. (Paper read to the Australian and New Zealand Association for the Advancement of Science.)

Nahas, G. G. (1950). Spectrophotometric determination of haemoglobin and oxyhaemoglobin in whole haemolyzed blood. *Science*, **113**, 723.

Turner, A. W., and Hodgetts, V. E. (1958). The red cell storage function of the spleen in sheep and its relation to fluctuation of jugular haematocrit variations. *Aust. J. exp. Biol. med. Sci.* (in press).

ASSOCIATION OF ANAESTHETISTS OF EDINBURGH

Notice

The following meetings will be held in the Royal College of Surgeons, Nicholson Street, Edinburgh, at 7.45 p.m.

Tuesday, December 9, 1958.	"Halothane." Drs. C. T. Barry and J. D. Robertson.
Tuesday, February 10, 1959.	"The Value of the Respiratory Function Test in Assessing a Patient for Surgical Operation." Dr. I. W. B. Grant.

Brit. J. Anaesth. (1958), **30**, 515

THE EFFECTS OF INTRAVENOUSLY ADMINISTERED DIHYDROCODEINE BITARTRATE IN ANAESTHETIZED MAN

BY

MARK SWERDLOW

Department of Anaesthesia, Salford Royal Hospital, Manchester, England

AND

FRANCIS F. FOLDES

Department of Anesthesia, Mercy Hospital, Pittsburgh, Pa., U.S.A.

IN the past decade narcotic analgesics have been widely used to supplement thiopentone-nitrous oxide-oxygen anaesthesia. Pethidine (Neff, Mayer and Perales, 1947) and alphaprodine (Siker, Foldes, Pahk and Swerdlow, 1954) have been most frequently employed, but many other narcotics, e.g. levorphanol (Brotman, Cullen and Wilkins, 1950) and anileridine (Riffin et al., 1958) have also been used. In the dosage necessary to produce adequate operating conditions, with small doses of thiopentone and muscle relaxants, these drugs frequently cause respiratory depression of variable intensity (Foldes et al., 1956). On the other hand, little or no circulatory changes have been observed when such techniques are employed (Foldes et al., 1957).

In view of the undesirable respiratory effects of narcotics when used for the supplementation of anaesthesia, the search has continued for a potent narcotic analgesic which would be free from this disadvantage. It has been reported that, in 30 mg subcutaneous doses, dihydrocodeine bitartrate produces relief of postoperative pain comparable with that given by 10 mg morphine, without causing appreciable respiratory depression (Gravenstein et al., 1956). Other investigators (Keats et al., 1957; Wallenstein et al., 1957) found that about 60 mg dihydrocodeine had the same analgesic potency as 10 mg morphine and that when used in this ratio the respiratory depression caused by the two analgesics was very similar (Seed et al., 1957). Eckenhoff and Helrich (1957) found relatively less respiratory depression after intramuscular injection of 50–60 mg dihydrocodeine than after comparable doses of other narcotic analgesics. In an earlier study one of us observed (Swerdlow, 1957) that the intravenous injection of 0.25 to 0.5 mg/kg dihydrocodeine bitartrate in patients anaesthetized with 8 mg/kg thiopentone sodium and nitrous oxide-oxygen produced less depression of respiration rate and minute volume than 0.6 mg/kg pethidine. However, in the course of these and other observations it became evident that relatively larger doses of dihydrocodeine than of pethidine are necessary to provide adequate analgesic supplementation of clinical anaesthesia. Consequently, a study was undertaken of the circulatory, respiratory and other effects of dihydrocodeine bitartrate in anaesthetized subjects.

PART I

MATERIAL AND METHOD

Circulatory and respiratory studies were carried out on 19 subjects, 9 males and 10 females. Their ages ranged from 19 to 52 years; the average age was 31 years. All were relatively fit patients who were to be operated on for minor surgical conditions which did not affect their general health. They were premedicated with 8–11 mg morphine and 0.6 mg atropine injected subcutaneously 45–60 minutes before the start of anaesthesia. In the anaesthetic room the patients were lightly anaesthetized with thiopentone sodium and nitrous oxide-oxygen according to a previously described technique (Foldes et al., 1952). When the level of anaesthesia became stabilized pulse rate, blood pressure, respiratory rate and respiratory minute volume* were deter-

* Minute volume was measured with a Bennett ventilation meter inserted in the circle absorption system.

mined. These measurements were used as control values. Following this, at zero time, 1.5 mg/kg dihydrocodeine bitartrate was injected intravenously in 30 seconds. All measurements were repeated at 3, 6, 10 and 15 minutes after the injection of dihydrocodeine. Tidal volume was calculated from respiratory rate and minute volume. In addition to these objective measurements observations were made on the presence or absence of skin changes attributable to histamine release, and of central nervous system stimulation (e.g. awakening, movement of extremities, coughing, etc.).

The respiratory changes were expressed as per cent of control values, and the absolute values of the circulatory changes were recorded.

RESULTS

The observations made on the respiratory and circulatory changes are summarized in tables I and II respectively. It is evident from table I that the injection of 1.5 mg/kg dihydrocodeine caused a statistically significant ($p<0.001$) decrease of the respiratory rate. This decrease was 20.5 per cent 3 minutes after the injection of the drug and reached its maximum (35.9 per cent) at 15 minutes. There was a compensatory increase in the tidal volume which amounted to 5 per cent at 3 minutes and reached its maximum (55.8 per cent) at 15 minutes. The tidal volume changes were statistically significant from 6 minutes onwards. There was a moderate, but not significant, decrease in minute volume in the first 10 minutes but by 15 minutes after the drug administration the minute volume had returned to control level.

In contrast to the relatively minor changes in the respiratory parameters, marked circulatory changes were present throughout the 15-minute observation period. There was a statistically significant ($p<0.001$) increase of the pulse rate and decrease of both the systolic and diastolic blood pressure. The circulatory changes were most marked at 3 minutes when the average increase in pulse rate was 26 per cent, and the average systolic and diastolic blood pressure decreased by 47 and 52 per cent respectively. The circulatory measurements tended to return towards normal with time but were still significantly different from control values at the end of the 15-minute observation period.

Side Effects

Of the 19 patients included in the respiratory and circulatory study 16 showed signs suggestive of histamine release immediately following the intravenous injection of dihydrocodeine. These signs, noted earlier by Swerdlow (1957), included wealing along the course of the vein into which the injection was made, generalized "goose pimples", and marked reddening of the face, neck and upper part of chest. Seven of the 19 patients coughed after injection of dihydrocodeine and 13 showed various signs of transient central nervous system stimulation.

PART II

METHOD OF EVALUATION OF ANALGESIC POTENCY

In 7 of the 19 patients included in the studies described surgical incision was made within a few minutes of the end of the experimental measurements (i.e. 18–26 minutes after administration of 1.5 mg/kg dihydrocodeine). Analgesia was satisfactory in only 3 of the 7 patients; the others resented the skin incision and required supplementary doses of dihydrocodeine or of thiopentone before it was possible to proceed with the operation.

In 35 patients dihydrocodeine was used as an analgesic supplement to anaesthesia consisting of a sleep dose of thiopentone followed by nitrous oxide-oxygen (6l.:2l.) and when necessary small doses of muscle relaxants. These 35 patients were undergoing a variety of operations including appendicectomy, herniorrhaphy, partial gastrectomy and orthopaedic surgery. An initial dose of 20 mg dihydrocodeine was usually employed followed by supplementary doses of 10–20 mg. Despite preliminary spraying of the cords with a local analgesic and the use of an analgesic cream on the endotracheal tube, the patients frequently demonstrated a persistent objection to the presence of the tube. It was found much easier to maintain smooth and satisfactory anaesthesia with regular, adequate respirations if an endotracheal tube was not employed.

Postoperative recovery of consciousness was rapid, the cough reflex being uniformly present at the termination of surgery and in most cases patients were capable of answering simple questions within 5 minutes of discontinuing the

TABLE I

The effects of Dihydrocodeine Tartrate on Respiratory Rate, Tidal Volume and Minute Volume expressed in per cent of Control Values.

Time in minutes after administration	Respiratory rate			Tidal volume			Minute volume		
	Mean	St. error	P	Mean	St. error	P	Mean	St. error	P
0	100.0	—	—	100.0	—	—	100.0	—	—
3	79.4	3.6	<0.001	105.8	11.1	n.s.	89.8	10.6	n.s.
6	74.1	4.1	<0.001	118.7	8.9	<0.05	88.9	8.3	n.s.
10	67.4	3.7	<0.001	141.4	4.7	<0.001	91.9	7.0	n.s.
15	64.1	4.3	<0.001	155.8	10.3	<0.001	99.0	9.3	n.s.

TABLE II

The effects of Dihydrocodeine Tartrate on Pulse and Blood Pressure.

Time in minutes after administration	Pulse rate			Systolic pressure			Diastolic pressure		
	Mean	St. error	P	Mean	St. error	P	Mean	St. error	P
0	96.7	3.6	—	115.8	4.0	—	73.2	2.5	—
3	125.0	5.5	<0.001	61.6	5.9	<0.001	35.3	3.4	<0.001
6	123.7	5.2	<0.001	67.4	4.7	<0.001	41.4	3.7	<0.001
10	115.1	4.3	<0.001	77.9	4.9	<0.001	46.4	3.6	<0.001
15	106.6	5.0	n.s.	84.7	4.8	<0.001	51.1	4.1	<0.001

administration of nitrous oxide and oxygen. The respiration rate tended to be rather rapid throughout anaesthesia and there was commonly an increase in pulse rate, but the blood pressure did not show any regular trend.

No marked ill effects were noted on careful follow-up in any of the patients in this study. In one patient, however, a diffuse rash developed over the whole body, without any apparent cause, 2 hours after appendicectomy. The rash disappeared promptly on antihistamine treatment.

DISCUSSION

The respiratory changes observed after intravenous injection of dihydrocodeine were less marked than those caused by comparable intravenous doses of other analgesics (Foldes et al., 1957); this was also reported by Eckenhoff et al. (1957), who administered dihydrocodeine by the intramuscular route. Unlike other narcotic analgesics which cause maximal respiratory depression within 2–5 minutes after intravenous administration, dihydrocodeine caused a slowing of the respiratory rate which did not reach its nadir until 15 minutes after its administration. We have no definite explanation for this unusual phenomenon, but it may have resulted from breath-holding due to lightness of anaesthesia with dihydrocodeine. As with other analgesics the compensatory increase in tidal volume became progressively greater throughout the observation period and minute volume had returned to control level by the end of 15 minutes. In contrast to this the circulatory effects of large intravenous doses of dihydrocodeine were more pronounced and persistent than those seen after comparable doses of other narcotic analgesics.

Of the 19 patients in whom respiratory and circulatory changes were followed closely, the lowest systolic blood pressure could not be measured in 3, nor the diastolic blood pressure in 9 patients. Return of blood pressure to control values was slow and the systolic pressure was 70 or less in 5 of the 19 patients. The intravenous administration of antihistaminics had no effect on the hypotension but the blood pressure responded promptly to intravenous methoxamine. Considering that these dramatic circulatory changes occurred in relatively young and fit individuals it is evident that the intravenous administration of a large dose of dihydrocodeine might have disastrous consequences in anaesthetized patients with known or latent myocardial insufficiency. Other disturbing findings were the high incidence of signs and symptoms suggestive of histamine release and central nervous system stimulation. Besides the skin changes described, bronchiolar spasm was encountered in 2 patients and an asthmatic type of breathing with prolonged expiratory phase in several others. The incidence and intensity of signs of central nervous system stimulation were also alarming. These effects, seldom seen with other narcotic analgesics, were described for dihydrocodeine in 1934 by Eddy and Small.

Based on its ability to relieve postoperative pain (Keats et al., 1957) or chronic pain caused by cancer (Wallenstein et al., 1957), 60 mg and 68 mg dihydrocodeine respectively were reported to be equivalent to 10 mg of morphine. Assuming the generally accepted 10:1 ratio between the analgesic potency of morphine and pethidine, 68 mg dihydrocodeine should be equivalent to 100 mg of pethidine. The analgesic potency of 1.5 mg/kg dihydrocodeine would thus be equivalent to that of 2.25 mg/kg of pethidine. In fact, the analgesic potency of this dose of dihydrocodeine as measured by its effectiveness as a supplement to thiopentone-nitrous oxide-oxygen anaesthesia is considerably less than that of 1.0 mg/kg pethidine. It is interesting to note in the present work that the analgesia obtained with the smaller doses of dihydrocodeine was not inferior to that found with 1.5 mg/kg doses. This observation is in agreement with the report of Keats and his colleagues (1957) that on subcutaneous administration 30 mg dihydrocodeine is only 9 per cent less effective than 60 mg and no greater analgesia can be obtained by increasing the dose to 90 mg. It is possible that in larger doses the central nervous system stimulating action of dihydrocodeine antagonizes its analgesic effect, thus preventing an increased analgesic response.

Because of its undesirable circulatory effects, its histamine-releasing and central nervous system stimulating properties, and its relatively weak analgesic potency, dihydrocodeine bitartrate was not found to be a satisfactory supplement to thiopentone-nitrous oxide-oxygen anaesthesia. This does not necessarily imply that dihydrocodeine has no place in the management of pain in con-

scious patients. Since, even in large intravenous doses, it causes relatively little respiratory depression and no marked circulatory changes have been reported following its subcutaneous or intramuscular administration in smaller but analgesic doses, its use does not seem to be contra-indicated in relatively fit individuals. Indeed, there is evidence (Dundee, 1957) that it may be an agent of some value in chronic pain. However, further studies will be necessary to determine whether it can be safely used in patients with disorders of the cardiovascular system and in allergic individuals.

SUMMARY

The circulatory and respiratory effects of 1.5 mg/kg dihydrocodeine administered intravenously were investigated in 19 lightly anaesthetized subjects.

There was a significant decrease in the respiratory rate and increase in the tidal volume; these changes reached their maximum 15 minutes after administration of the drug. Because of the compensatory nature of these changes, the effect on minute volume was relatively small.

There was a marked increase in pulse rate and a precipitous drop in both systolic and diastolic blood pressure. These changes were maximal 3 minutes after injection of the drug and later readings showed a trend to return towards control levels.

In the majority of patients the intravenous injection of dihydrocodeine was followed by various signs and symptoms of histamine release and of central nervous system stimulation.

In 7 of the patients who received 1.5 mg/kg and in 35 patients who received smaller doses of dihydrocodeine the efficacy of this analgesic as a supplement to thiopentone-nitrous oxide-oxygen was observed.

As measured by the ability of lightly anaesthetized patients to tolerate skin incision and surgery the intensity of analgesia obtained by intravenously administered doses of dihydrocodeine was less than that of comparable doses of pethidine or alphaprodine.

The results of this investigation indicate that when administered in large intravenous doses to anaesthetized patients dihydrocodeine causes unwanted side effects. It was also found that dihydrocodeine is not a satisfactory supplement to thiopentone-nitrous oxide-oxygen anaesthesia.

ACKNOWLEDGMENT

We would like to express our gratitude to Dr. E. C. Cockings, Resident Anaesthetist at Salford Royal Hospital, for his considerable practical assistance in these studies.

REFERENCES

Brotman, M., Cullen, S. C., and Wilkins, D. S. (1950). Intravenous supplementation during nitrous oxide anaesthesia; comparison of demerol, morphine and a new potent analgesic drug (15431). *Anesthesiology*, **11**, 527.

Dundee, J. W. (1957). Silver Jubilee Meeting, Association of Anaesthetists, London.

Eckenhoff, J. E., and Helrich, M. (1957). The effect of dihydrocodeine on the respiration and circulation in man. *Anesthesiology*, **18**, 891.

Eddy, N. B., and Small, L. F. (1934). Studies of morphine, codeine and their derivatives, IV: Hydrogenated codeine isomers. *J. Pharmacol. exp. Ther.*, **51**, 35.

Foldes, F. F., Ceravolo, A. J., and Carpenter, S. L. (1952). The administration of nitrous oxide-oxygen anesthesia in closed systems. *Ann. Surg.*, **136**, 978.

—— Lipschitz, E. L., Weber, G. M., Swerdlow, M., and Pirk, L. A. (1956). Levallorphan (Lorfan) and alphaprodine (Nisentil) in anesthesia. *J. Amer. med. Ass.*, **160**, 168.

—— Zeedick, F. J., and Koukal, L. R. (1957). Effects of narcotic analgetics and narcotic antagonists on respiration. *Amer. J. Med. Sci.*, **233**, 153.

Gravenstein, J. S., Smith, G. M., Sphire, R. D., Isaacs, J. P., and Beecher, H. K. (1956). Dihydrocodeine. *New Engl. J. Med.*, **254**, 887.

Keats, A. S., Telford, J., and Kurosu, Y. (1957). Studies of analgesic drugs; dihydrocodeine. *J. Pharmacol. exp. Ther.*, **119**, 155.

Neff, W., Mayer, E. C., and Perales, M. de la Luz (1947). Nitrous oxide and oxygen anesthesia with curare relaxation. *Calif. Med.*, **66**, 67.

Riffin, I. M., Preisig, R., Wheaton, H. H., Landman, M., and Schwartz, B. (1958). Anileridin: its use in anaesthesia and for postoperative pain relief. *Curr. Res. Anesth.* (in press).

Seed, J. C., Wallenstein, S. L., Bellville, J. W., and Houde, R. W. (1957). Comparative respiratory depressant effects of dihydrocodeine and morphine. *J. Pharmacol. exp. Ther.*, **119**, 182.

Siker, E. S., Foldes, F. F., Pahk, N. M., and Swerdlow, M. (1954). Nisentil (1, 3, dimethyl-4-phenyl -4 propionoxy piperidine): a new supplement for nitrous oxide-oxygen thiopentone (pentothal sodium) anaesthesia. *Brit. J. Anaesth.*, **26**, 405.

Swerdlow, M. (1957). Dihydrocodeine. *Lancet*, **1**, 482.

Wallenstein, S. L., Seed, J. C., and Houde, R. W. (1957). Clinical assay of the relative analgesic potencies of dihydrocodeine and morphine. *J. Pharmacol. exp. Ther.*, **119**, 191.

Brit. J. Anaesth. (1958), **30**, 520

ANAESTHESIA FOR CONSERVATIVE LUNG RESECTION FOR CANCER

BY

A. R. HUNTER

Royal Infirmary, Manchester

THE mortality from pneumonectomy for lung cancer is considerable especially when it is performed in the elderly or relatively unfit. Price Thomas (1955) has described an operation designed to reduce this seriously high death rate. It consists essentially in removal of the lobe in which the cancer is growing, together with a portion of the main stem bronchus. The remainder of the lung is conserved and its bronchus is thereafter sutured to the main bronchial tree.

This procedure presents a number of serious problems to the anaesthetist. First, it is necessary that one main bronchus should, if required, be open for a period of up to an hour. Secondly, it greatly helps the surgeon if the lung on the operated side can be deflated, at will. It is most desirable that at the conclusion of the anastomosis any blood in the cavity of the bronchus should be removed by suction and the remaining lung thereafter inflated to fill the pleural cavity. The anastomosis line too must be tested for leakage under water by increasing the gas pressure in the bronchus. The ordinary problems of any chest operation—namely, the control of the spread of sputum, the prevention of mediastinal flap and of paradoxical respiration and the replacement of lost blood—are, of course, of the usual importance in these cases. Lastly, because the operation is often performed primarily because the patient is unfit for pneumonectomy, many of those undergoing it will be rather poor risks in a group of patients who are as a whole often far from well.

THE MECHANICAL PROBLEM

The primary problem in these cases is the maintenance of adequate ventilation after the opening of the bronchial tree. It is possible if no other means is available to use ordinary endotracheal anaesthesia in these cases and to occlude the opened bronchus with a light clamp such as that used for the auricle in mitral valvotomy. The instrument, however, tends to be in the surgeon's way and in any case many believe that even so light a clamp will impair the healing powers of the tissues of the bronchus. It is, however, important to know that this technique will work as there are cases where no other method of anaesthesia is feasible.

Secondly, it is possible to use an orthodox technique of contralateral endobronchial anaesthesia. In the case of an operation on the right lung this involves intubation of the left main bronchus with a suitable tube and the maintenance of anaesthesia using this lung only. Where the left lung is to be operated on, a blocker is placed in the left main bronchus and the right lung only used for anaesthesia which is maintained by the endotracheal route. These methods give perfectly satisfactory results save for one point. It is not easy to inflate and deflate with certainty the lung which is being operated on. The tubes which are especially designed for the purpose have a very narrow lumen to that side which is thus easily blocked by small amounts of sputum. Expansion of the lung then requires the application of dangerous pressure and deflation is nearly impossible.

The only apparatus which affords full control of both lungs during intrapulmonary surgery is the Carlens double lumen tube. With its aid it is possible to maintain endobronchial anaesthesia, using only the contralateral lung while the main bronchus is open. It is, however, also possible to open the chest under what is substantially endotracheal anaesthesia to both lungs and when the bronchial anastomosis is complete to inflate the remaining lobe on that side, to remove any blood or sputum from the bronchus and to test the tightness of the anastomosis by vigorous inflation before the chest is closed. Further, the functional

efficiency of the reconstituted bronchus may be tested. If air passes readily in and out of the remainder of the lung during inflation the suture line is satisfactory. If, however, there is a tendency to trapping of air blown into the conserved lobe, which is indicated when the lobe does not deflate immediately on reducing the pressure in it, the bronchus is either kinked or narrowed by a stitch. Re-anastomosis is then necessary.

A Carlens tube offers an additional advantage. When one lung is out of use for the period of endobronchial anaesthesia, it is allowed to collapse completely. The circulation through it is thus reduced to negligible proportions and shunting scarcely occurs at all. This period of anaesthesia should not therefore be associated with cyanosis. By contrast under endobronchial anaesthesia of the classical type the blocked-off lung remains expanded to a variable degree during the operation and the efficieny of ventilation is sharply diminished by circulatory shunting. In the elderly unfit type of patient in whom this operation is performed this cannot but have adverse effects on the general condition. Also blocking off one lung and collapsing it so that the circulation through it is reduced is substantially equivalent to a functional pneumonectomy. It is thus possible to carry out a rough-and-ready lung function test in cases where it is doubtful whether conservative resection or the more radical procedure of pneumonectomy is indicated by the pathological condition.

TECHNIQUE OF ANAESTHESIA

There is nothing original about the technique of anaesthesia employed. Patients are premedicated with papaveretum 20 mg and hyoscine 0.4 mg or with morphine 10 mg and atropine 0.6 mg, depending on their age and physical fitness. Anaesthesia is induced with thiopentone in a dose of 200 to 400 mg together with 30 to 50 mg of suxamethonium. After inflation of the lungs with oxygen the larynx is exposed with a Macintosh laryngoscope and it and the trachea are sprayed with 4 per cent lignocaine containing 1:40,000 adrenaline. The Carlens tube, which has previously had its cuffs tested for leaks under water, and has been freely lubricated with the proprietary 2 per cent lignocaine gel normally used for the urethra, is then passed by the method described by Jenkins (1956). As soon as the cuffs have been inflated and the patient connected to the anaesthetic machine, the connecting tubes to the Carlens are clipped off in turn and a test inflation of each lung is performed to make quite certain that the tube has been properly placed. Thereafter anaesthesia is maintained with nitrous oxide and oxygen together with suitable doses of pethidine and if necessary a little more thiopentone. A blood transfusion is set up before the operation begins. The patient is curarized with d-tubocurarine just before the chest is opened and spontaneous respiration is held in abeyance till the end of the thoracotomy by a combination of myoneural block and as much hyperventilation as is safe. Carbon dioxide absorption with Water's canister is used to facilitate this.

If at the end of the procedure spontaneous breathing is not restored spontaneously, a sharply limited amount of carbon dioxide is administered (10 breaths containing 20 per cent of the gas once only). If this fails to restart breathing 4 ml of nikethamide is injected intravenously. So far this has never failed the author as a means to restore some spontaneous respiration at the end of this or any other operation. When the returning respiration is inefficient sufficient atropine is given to accelerate the pulse visibly and neostigmine is given in a dose of 1.25 mg. If this does not restore full normal breathing an additional 1.25 mg of neostigmine is given with 0.6 mg of atropine in the same syringe.

It is important that full decurarization should be attained in these cases. They awake rapidly on withdrawing the anaesthetic and if the dyspnoea of residual curarization is superimposed on that of a major thoracotomy, their distress may be very great indeed. Secondly, as with every other chest operation, it is vitally important that the patient should be able to cough and thus to clear his bronchial tree as soon as possible after operation.

DIFFICULTIES

The whole question of the difficulties and dangers of the Carlens tube has been discussed at length by Jenkins and Clarke (1958) and indeed some of the cases mentioned in their paper form part of this series. There are, however, certain difficulties which assume a special importance in the patient who has one bronchus open. The first of these

is the development of a leak in a cuff. Nothing can in fact be done to anticipate this accident but it will be to some extent avoided if tubes are carefully tested for leaks under water before they are used. Fortunately it is usually the tracheal cuff which gives way and it is possible by pushing the lower jaw back and increasing the gas flow to compensate to some extent at least for the leak. Surgical puncture of the cuff in the left main bronchus is, of course, possible. If this occurs it may prove necessary to withdraw the Carlens tube part way as in left pneumonectomy and to use it simply as an endotracheal tube or to do as Jenkins and Clarke (1958) and replace it with an ordinary cuffed tube in the trachea. The open bronchus must then be clamped and the advantages of the Carlens tube are lost.

Another difficulty in the use of the Carlens tube is displacement of the cuff in the left main bronchus upwards into the trachea. It will often be noticed where the right main bronchus is opened that the hook is no longer in contact with the carina and that the tube has slipped a little way upwards. If during dissection considerable traction is exerted on the hilum of a left lung the relatively mobile bronchus may be dragged past the cuff. The tendency to slipping upwards is thus exaggerated and when the traction is released the cuff may come to lie partly in the lumen of the trachea where it blocks the gas flow to and from the right lung with the production of a total or near total respiratory obstruction there. The anaesthetist appreciates this as a gross increase in the resistance to inflating the right lung and a marked diminution in the return flow of gases when the pressure is released. The accumulation of sputum on the right side will produce the same effect but will usually be preceded by some moist sounds in the tube. Further, if the left cuff is blocking the airway it will usually be impossible to insinuate a suction catheter into the right main bronchus. If upward displacement of the left cuff has occurred the remedy is to stop the operation, deflate both the cuffs and push the Carlens tube down again until it occupies its proper position. The surgeon can give very considerable help both in the diagnosis and treatment of this condition by localizing the lower end of the Carlens tube by palpating it through the wall of the exposed bronchus. Indeed one of the most satisfactory things about the use of this apparatus is the fact that the surgeon can give the anaesthetist so much help in placing the tube in the position appropriate to the stage of the operation.

No sequelae traceable to the introduction of the Carlens tube were noted by Jenkins and Clarke (1958) in their large series nor have there been any in this smaller group. The only difficulty in the author's experience has been that in small women it may prove impossible to pass the size 37 tube beyond the cricoid ring. In such cases the bronchial anastomosis must be performed distal to an auricular clamp placed close to the bifurcation of the trachea, or better under formal endobronchial anaesthesia. There has been no suggestion in these or in any other cases that the passage of the Carlens tube has traumatized the larynx or trachea any more than an ordinary endotracheal tube.

The only real cause for anxiety has been the amount of pressure which it has been necessary to use when ventilating an isolated lung. As the compliance of a single lung ought in fact to be half that of two lungs it is only natural that double the pressure would be required to produce the same tidal exchanges. In a number of cases the inflation pressures were measured with the aid of a capacitance manometer and a 2:1 relationship between the applied pressures did in fact exist (table I).

TABLE I

Inflation pressures with Carlens tubes.

	Number of observations	Inflation pressure (mm Hg)
Inflating both sides	17	15.0 ± 3.8
Inflating one side only	14	26.5 ± 6.7

Many anaesthetists are concerned about the relative narrowness of the Carlens tube as a cause of these high inflation pressures but this is of minor importance compared with the reduction in compliance produced by cutting out one lung. In any case as far as the inspiratory stroke is concerned the anaesthetist's hand can compensate without difficulty for any resistance generated in the tube. The influence of the tube on expiration can largely be overcome by allowing a long ex-

piratory period for full passive deflation. Fortunately in the lateral position the weight of the mediastinal viscera aid in this process. This same pattern of inflation will serve to minimize the circulatory effects of the increased inflation pressure which in these circumstances can affect only the circulation in the pulmonary capillaries. The more serious disturbances due to the exertion of excessive pressure on a closed chest are due to interruption of the gradient on which the venous return depends, and cannot occur as long as one side of the mediastinum is at atmospheric pressure. In any case fall in systemic blood pressure and rise in pulse rate always provide a clear indication of upsets of the circulation due to overforcible inflation. In the cases of this series, however, the change from ordinary anaesthesia to that involving one lung only has not been associated with disturbances of this type.

The cases on which this report is based numbered 41 and the surgical results are being reported by Jones (1958) elsewhere. There was no mortality or morbidity in the postoperative period traceable to the anaesthesia.

ACKNOWLEDGMENTS

My thanks are due to Mr. P. H. Jones for his understanding co-operation in this most interesting work, and to the many registrars, including Drs. Jenkins and Clarke, who during the past two years have been associated with me at the Manchester Regional Chest Centre at Baguley.

REFERENCES

Jenkins, A. V. (1956). Carlens catheter: a simple method of intubation. *Brit. J. Anaesth.*, **28**, 85.
—— Clarke, G. (1958). Endobronchial anaesthesia with the Carlens catheter. *Brit. J. Anaesth.*, **30**, 13.
Jones, P. H. (1958). (To be published.)
Thomas, C. Price (1956). Conservative resection of the bronchial tree. *J. roy. Coll. Surg. Edinb.*, **1**, 169.

ROYAL VICTORIA HOSPITAL, McGILL UNIVERSITY, MONTREAL

Abbott Research Fellowship in Anaesthesia

Applications are invited for the above position from anaesthetists of senior registrar status to carry out a programme of clinical research. Salary $7200 per annum for one year. Applications (3 copies) with photograph and the names of three referees should be submitted to the undersigned before January 31, 1959, from whom particulars can be obtained.

DR. A. B. NOBLE
Director of Anaesthesia, Royal Victoria Hospital,
and
Assistant Professor of Anaesthesia, McGill University.

Brit. J. Anaesth. (1958), **30**, 524

TRANSLUMBAR AORTOGRAPHY—ITS HAZARDS IN RELATION TO ANAESTHESIA

BY

PETER STUART

Department of Anaesthetics, Glasgow Royal Infirmary, Scotland

TRANSLUMBAR aortography was first described by the Portuguese urologist, Dos Santos, in a report to the Surgical Society of Paris in 1929 (Dos Santos, 1929). It is only in more recent years, however, that the technical development of this procedure has reached a stage where its safety and simplicity have been such as to elicit a more widespread interest in its diagnostic applications. Although outstanding results have been reported by workers both in this country and abroad, establishing the value of aortography as a clinical diagnostic procedure (Nelson, 1942; Leriche, 1952; Stirling, 1957), it is still true to say that the frequency and extent of its application are mainly limited by the risks involved. McAfee and Willson (1956) in a review of the complications of aortography testify to the hazards of anaesthesia and would appear to serve an indictment against the use of general anaesthesia for this procedure. As they are not alone in expressing such sentiments (Deterling, 1952), a reappraisal of the anaesthetic methods commonly employed would appear desirable, with particular reference to the complications of this procedure.

Translumbar aortography may be regarded as one of a specialized group of vascular visualization procedures comprising the radiological examination of the abdominal aorta and its major branches after injection of a suitable contrast medium through a needle introduced into the vessel by the translumbar route.

As a diagnostic refinement, the procedure has found its main application in urological and vascular surgery although it has also been utilized to locate placental position in suspected placenta praevia. Aortography should never be considered a minor surgical procedure (Leriche, 1952) nor should it be employed simply as a means of satisfying "the physician's curiosity in his differential diagnostic programme" (Smith et al., 1951). In fact Leriche categorically states that in peripheral vascular disease aortography should only be employed if resection or reconstructive surgery of the vascular lesion is to be considered. Although a detailed account of the wide variations in the surgical and radiological technique is beyond the scope of this communication, it is necessary to consider briefly several controversial features of the procedure as a prelude to an appreciation of the anaesthetic problems involved.

CONTRAST MEDIUM

The continued interest shown in the use of new contrast media for this radiographic examination suggests that no entirely satisfactory substance has yet been evolved, although vascular visualization was first accomplished (Haschek and Lindenthal, 1896) within a short time of Röntgen's epoch-making discovery in 1895. Although the modern organic iodides have now almost completely supplanted the original use of sodium iodide in this field, possible toxic effects from these opaque media still constitute a real danger. With regard to sensitivity, the inclusion of promethazine in the pre-operative preparation of the patient, together with the routine use of an intravenous test dose of the medium (1–2 ml) administered 5 to 10 minutes prior to induction of anaesthesia with subsequent check on blood pressure and pulse rate, will eliminate any serious hazard from this source (Stirling, 1957).

All the opaque media in current use, whether of the organic or inorganic variety, must be regarded as chemotoxic to nervous tissue and even one of the most recent to receive favourable comment—sodium acetrizoate—has been the subject of a communication regarding its chemotoxic properties (Tarazi et al., 1956). The

implications arising from this fact and their bearing on the choice of anaesthesia are discussed more fully below.

Irrespective of the medium used, and even with such recent compounds as sodium acetrizoate, some degree of sensory stimulation is elicited on rapid intra-aortic injection, although not of the intensity formerly obtaining with sodium iodide. The discomfort (heat) experienced by the conscious patient may lead to sudden movement at a critical phase of the procedure and constitutes the main objection to local anaesthetic techniques.

TECHNIQUE OF INJECTION

In addition to toxicity of the contrast medium as an undoubted cause of many of the reported complications following aortography, the mode of injection per se is now regarded by many as a significant factor (Leriche, 1952; Crawford et al., 1957). While some authorities condemn any form of pressure device as a possible cause of neurological disaster (Sutton, 1957), other workers, although not condoning the use of high pressure gas-air machines, have pointed out the relative advantages and safety of a simple hand operated pump (Stirling, 1955). In this connection a recent report (Gaylis and Laws, 1956) has served to illustrate the danger of intramural extravasation as a further hazard during injection, emphasizing its possible significance in relation to neurological sequelae.

In addition to thirteen cases of paraplegia following aortography, a review of the literature would indicate a formidable list of other reported complications. Although some of these lie outside the scope of this communication, it is pertinent to note the occurrence of such hazards as aortic dissection, extra-aortic extravasation, perithecal injection, haemorrhage, and pneumothorax.

ANAESTHESIA

The following brief review illustrates the widely conflicting opinions expressed in recent reports on anaesthetic methods for this procedure and serves to indicate the necessary criteria for adoption of a suitable anaesthetic technique.

Spinal Analgesia.

This is widely regarded as the method of choice in the United States (Adriani and Roman, 1948; Feldman et al., 1954) where amethocaine hydrochloride (Pontocaine) is commonly employed in either a hypobaric or hyperbaric solution. As complete sensory analgesia for this procedure demands a block to the level of the fifth thoracic segment, some degree of hypotension is inevitable, necessitating the judicious administration of a vasopressor agent. In an effort to overcome this objection, recent reports have advocated use of the drug lucaine hydrochloride (β-2-piperidyl-ethyl-ortho-amino-benzoate hydrochloride) in hypobaric solution for the production of sensory subarachnoid block without significant motor paralysis (Feldman, 1954; Greene et al., 1956).

The most serious objection to spinal analgesia, however, only becomes apparent when its possible risks are equated against the reported complications from aortography per se. Paraplegia or any of the diversified features of the cauda equina syndrome have been attributed to errors in the technique of spinal analgesia so that complete exoneration of the spinal technique would be virtually impossible to establish. In the light of these considerations translumbar aortography should be considered a contra-indication to the use of spinal analgesia.

Epidural Analgesia.

Although capable of producing satisfactory results (Feldman, 1954), the main disadvantages of this technique are associated with the delay in onset of analgesia, and the rather high failure rate in any but the most expert hands. Where analgesia is limited to a purely sensory block without significant motor paralysis, hypotension is unlikely to be a troublesome feature. A more serious objection to this technique, as with spinal analgesia, concerns the medico-legal considerations which would undoubtedly apply in the event of neurological sequelae, and in these circumstances epidural analgesia cannot be regarded as the method of choice.

Local Infiltration and Paravertebral Block.

The advocates of local infiltration, either alone or in combination with paravertebral block, claim that this method constitutes the safest approach to anaesthesia for translumbar aortography (Deterling, 1952; Thornton, 1957). It is unlikely, however, that even the premedicated patient will regard paravertebral block as other than an un-

pleasant and trying experience. Despite the claims of safety to the patient based on the strictly limited disturbance to normal physiology, the method fails to achieve its primary function of adequate sensory loss, particularly during pressure injection when the degree of sensory stimulation is undoubtedly greater than with the slower manual method. This failure to ensure complete immobility of the patient during the critical phase of the procedure constitutes the main disadvantage of the method.

Thiopentone Sodium.

When the pharmacological limitations of this drug are ignored, it is not surprising that the results achieved by its use as the sole anaesthetic agent for aortography should be described in rather dubious terms (Smith, 1951; Deterling, 1952; McAfee and Willson, 1956). The absence of adequate respiratory control in the prone position associated with such risks as coughing and laryngospasm are sufficient reasons in themselves to prejudice this technique without the additional factor of lack of analgesic potency. It is perhaps no mere coincidence that extra-aortic extravasation has been the complication most frequently encountered with this technique of anaesthesia, which would appear to contribute more to the hazards of aortography than to its safety.

General Anaesthesia.

The adoption of the prone position for injection can be regarded as the only standardized part of this procedure which in other respects of its performance may vary between wide limits. Some workers recommend a control radiograph after positioning the patient and before insertion of the needle (Smith, 1952; Deterling, 1952); others stress the importance of a test injection and preliminary radiograph to ascertain the exact position of the needle in the aorta (Deterling, 1952; Crawford, 1957; Hare, 1957). A pressure device may be used for injection (Stirling, 1955; Gaylis and Laws, 1956), or the latter may be performed simultaneously through two needles, while radiography may involve a single or multiple film exposure technique. For the anaesthetist faced with the possible permutations and combinations of these variables, an unobstructed airway, control of respiration, and adequate analgesia are the basic criteria for success.

Endotracheal intubation with a cuffed tube avoids the dangers of respiratory obstruction in the prone position and is facilitated after induction with thiopentone by use of a small dose of suxamethonium hydrochloride (25–50 mg), the larynx and trachea being sprayed with lignocaine before insertion of the tube.

After positioning the patient and before insertion of the aortic needle, apnoea and controlled respiration are established by a further injection of suxamethonium, some estimate of the dose required being derived from the duration of apnoea following intubation. During introduction of the aortic needle, vigorous artificial ventilation is undesirable, particularly in cases of high aortic puncture where it may contribute to the risk of pneumothorax, a complication not unknown as a sequel to aortography. As nitrous oxide alone is unlikely to provide adequate analgesia especially where pressure injection of the contrast medium is employed, it is wiser to supplement the mixture rather than attempt to reinforce the lack of analgesic potency by vigorous ventilation and inactivation of the Hering-Breuer mechanism. Trichloroethylene may be added to the mixture of gases or pethidine may be used in preference and administered intravenously a few minutes prior to induction, thus ensuring maximum analgesic effect at the time of aortic puncture and injection.

Inadequate analgesia can scarcely be regarded as justification for recommending the use of a malleable needle "which would bend, in case the patient moved suddenly, while the needle was in the aorta" (Deterling, 1952), but rather as an indication of the need for reinforcing the anaesthetic mixture.

Experience at this medical centre now extends to over 1,000 cases of translumbar aortography mainly performed as an aid to urological diagnosis and to a lesser extent for investigation of peripheral vascular disease. The technical results achieved have recently been described in a monograph by Stirling (1957).

Pressure injection of the contrast medium by a simple lever device (Stirling, 1955) has been employed in almost all cases.

Local anaesthesia was favoured initially but soon abandoned when it proved unsatisfactory for the reasons already mentioned. In the remainder

satisfactory conditions have been consistently produced with a general anaesthetic technique based on the criteria described. There has been no significant postanaesthetic morbidity, nor has the technique contributed in any way to the incidence of postoperative sequelae.

CONCLUSIONS

It is perhaps significant that first reports on aortography did not appear in this country for more than twenty years after the original work of Dos Santos and his colleagues, and according to Leriche (1952) considerable controversy still exists as to the value versus the dangers of this procedure.

With the tremendous advances in cardiac and vascular surgery of the last decade, however, a renewed interest has developed in the diagnostic value of translumbar aortography and allied vascular visualization procedures, and it is highly probable that further study will bring forth even broader applications of these procedures. In these circumstances it is regrettable that the problems presented in anaesthetic management "have not been solved, despite the currently popular use of intravenous or local anaesthesia" (Feldman, 1954). It would appear that the end result in many instances has been a substantial contribution to the hazards of aortography rather than to its safety.

SUMMARY

As a result of experience gained, both in this country and the United States, of various anaesthetic techniques for translumbar aortography a critical review of current anaesthetic methods has been presented, in relation to the known hazards of the procedure, and the rationale of certain popular techniques has been questioned.

ACKNOWLEDGMENTS

It is a pleasure to record my appreciation of the interest shown by Dr. Vernon D. Thomas, Professor of Anesthesiology at the University of Rochester, New York, in permitting me to gain personal experience of various anaesthetic techniques for aortography during tenure of an appointment as Visiting Instructor in Anesthesiology. I thank Dr. A. C. Forrester, Senior Lecturer in Anaesthetics at the University of Glasgow for his encouragement in the preparation of this paper.

REFERENCES

Adriani, J., and Roman, D. A. (1948). Lucaine as spinal anaesthetic agent for urological surgery. *Urol. Cutan. Rev.*, **52**, 653.

Crawford, E. S., Beall, A. C., Moyer, J. H., and De Bakey, M. E. (1957). Complications of aortography. *Surg. Gynec. Obstet.*, **104**, 129.

Deterling, R. A. jr. (1952). Direct and retrograde aortography. *Surgery*, **31**, 88.

Dos Santos, R., Lamas, C., and Caldos, P. (1929). L'Arteriographie des membres. L'aorte et ses branches abdominales. *Med. Contemp.*, **47**, 93.

Feldman, E., Greene, B. A., and Chinn, H. Y. H. (1954). Spinal analgesia for trans-lumbar aortography. *Anesthesiology*, **15**, 66.

Gaylis, H., and Laws, J. W. (1956). Dissection of aorta as a complication of trans-lumbar aortography. *Brit. med. J.*, **2**, 1141.

Greene, B. A., Berkowitz, S., Feldman, E., Goldsmith, M., and Robbins, B. (1956). Spinal analgesia with lucaine; a critical appraisal based on 6,000 cases. *Anesthesiology*, **17**, 165.

Hare, W. S. C. (1957). Trans-lumbar aortography. *Brit. med. J.*, **1**, 518.

Haschek, E., and Lindenthal, O. T. (1896). Ein beitrag zur praktischen verwerthung der photographie nach Röntgen. *Wien. klin. Wschr.*, **9**, 63.

Leriche, R., Beaconsfield, P., and Boëly, C. (1952). Aortography; its interpretation and value. *Surg. Gynec. Obstet.*, **94**, 83.

McAfee, J. G., and Willson, J. K. V. (1956). A review of the complications of trans-lumbar aortography. *Amer. J. Roentgenol.*, **75**, 956.

Nelson, O. A. (1942). Arteriography of abdominal organs by aortic injection. *Surg. Gynec. Obstet.*, **74**, 655.

Smith, P. G., Rush, T. W., and Evans, A. T. (1951). Evaluation of trans-lumbar arteriography. *J. Urol. (Baltimore)*, **65**, 911.

Stirling, W. B. (1955). An aid to aortography. *Proc. roy. Soc. Med.*, **48**, 823.

—— (1957). *Aortography*, 1st. ed. Edinburgh and London: E. & S. Livingstone.

Sutton, D. (1957). Translumbar aortography. *Brit. med. J.*, **1**, 225.

Tarazi, A. K., Margolis, G., and Grimson, K. S. (1956). Spinal cord lesions produced by aortography in dogs. *Arch. Surg.*, **72**, 38.

Thornton, H. L. (1957). Anaesthesia for aortic reconstruction. *Brit. med. J.*, **1**, 253.

Brit. J. Anaesth. (1958), **30**, 528

PECAZINE (PACATAL) IN ABDOMINAL SURGERY

BY

E. R. S. HOOPER*

Late of Anaesthetic Department, United Cambridge Hospitals

PECAZINE is the hydrochloride or acetate of a synthetic phenothiazine derivative, N-methyl piperidyl-3-methyl phenothiazine (Pacatal, Mepazine), developed in Germany by Nieschulz et al., in 1954. The hydrochloride is presented in tablets for oral administration, while the more soluble acetate is used for injection. It is said to produce a balanced autonomic ganglion blockade of both the sympathetic and parasympathetic systems. It protects the heart against arrhythmias and cardiac arrest and the lungs against pulmonary oedema (Déchêne, 1956). The vomiting centre and the heat regulating centre are depressed and salivary and bronchial secretions are diminished. It potentiates the action of analgesics and general anaesthetics and has local anaesthetic properties of its own. It is quickly eliminated in the body. In 1956 Davies et al. commented favourably on its lack of unpleasant side-effects compared with chlorpromazine.

OBJECT OF TRIAL

This was to use pecazine as the sole supplement to thiopentone–relaxant–nitrous oxide–oxygen anaesthesia in abdominal surgery and to discover if the procedure was satisfactory and safe for routine administration.

In this series pecazine was not given prior to induction or postoperatively, but only intravenously during the course of general anaesthesia. It was considered that the period of time during which the patient might be affected by pecazine was during anaesthesia and up to 6 hours afterwards.

DATA

Selection of cases.

At first only comparatively fit patients were given pecazine. With increased experience, however, no selection took place, beyond excluding the very young. Many of the patients were elderly and some were gravely ill.

Age distribution.

This is shown in table I. The youngest patient was 8 years and the eldest was 86.

TABLE I

Age distribution

Age in years	No. of cases
8–15	23
16–29	36
30–49	71
50–65	74
66–86	31
Total	235

Cases.

These are listed in table II.

Premedication.

This is detailed in table III. All premedicant drugs were given approximately 1 hour preoperatively.

Strength of pecazine solution.

The 2-ml ampoules of pecazine were diluted to 10 ml with distilled water, giving an 0.5 per cent solution (5 mg/ml).

Relaxants.

In adults, suxamethonium chloride (Scoline) was used for intubation and d-tubocurarine (Tubarine) for maintenance. In children gallamine triethiodide (Flaxedil) was used throughout. Atropine and neostigmine were given at the end of operation in every case.

Anaesthetic technique

The patients were induced with thiopentone sodium and a relaxant, ventilated with oxygen and intubated. The dose of thiopentone varied

* Now at Lichfield Hospital, Lichfield, Staffs.

TABLE II
Cases

Nature of operation	Number of cases
Gastrectomy (various types)	36
Gastrectomy + splenectomy	2
Gastrojejunostomy	2
Perforated peptic ulcer	6
Hiatus hernia	1
Biliary tract	20
Entero-enterostomy	1
Ileostomy	3
Intussusception	1
Internal hernia with small gut obstruction	2
Appendicectomy	68
Colectomy (various amounts)	10
Colotomy, removal of polyp	1
Perforated diverticulum	1
Laparotomy and colostomy	6
Abdomino-perineal excision of rectum	7
Umbilical hernia	3
Inguinal hernia	17
Inguinal hernia (strangulated)	2
Femoral hernia	3
Femoral hernia (strangulated)	2
Division of adhesions	3
Laparotomy and exploration only	9
Abdominal abscesses	3
Gynaecology	18
Prostatectomy	4
Kidney	2
Iliac artery embolectomy	1
Lumbar sympathectomy	1
Total	235

TABLE III
Premedication

Age in years	Premedication
8–12	Nepenthe 1 minim (0.06 ml) per year of age Atropine 0.65 mg
13–15	Morphine 8.0 mg Atropine 0.65 mg
16–60	Papaveretum 22.0 mg Hyoscine 0.43 mg
60+	Morphine 11.0 mg Atropine 0.65 mg

from 150 to 500 mg, being that amount which produced sleep. One case, a healthy young man, required 750 mg. In adults, the initial dose of pecazine was given when the effect of suxamethonium had worn off, and was followed by a paralyzing dose of tubocurarine. Controlled respiration was maintained until the end of the operation with oxygen and nitrous oxide in the ratio of 2:5, using a Water's canister and a semi-closed circuit. The respiratory rate for adults during the first 5–10 minutes was 20/minute, towards the end of which period the patient was transferred to the operating theatre. Then the rate was lowered to 16/minute and the operation commenced. The rates for children were higher. In many cases the respiration was performed by a Fazakerley respirator, which has a negative phase at the beginning of expiration. This is particularly beneficial in paralyzed emphysematous patients.

The basis of the dosage of pecazine is shown in table IV. The maximum dose given was 50 mg, reached in 1 hour after the initial injection with the average adult male. The rate of dosage was varied occasionally, but not the maximum amount.

TABLE IV
Dosage

	Pecazine	
Age in years	Initial dose	Subsequent doses
Under 16	10 mg i.v.	10 mg i.v. every 20 min
16+, female	15 mg i.v.	10 mg i.v. every 20 min
16+, male	20 mg i.v.	10 mg i.v. every 20 min

Additional relaxant was given when necessary, with the proviso that none was administered within 20 minutes of the end of the operation, where that might be calculated.

When time permitted, blood pressure and pulse readings were taken as follows:

(1) In the ward before administering pre-operative medication.
(2) On arrival in the anaesthetic room.
(3) After intubation, before giving pecazine.
(4) 2–5 minutes after giving pecazine.
(5) Immediately before incision.
(6) Thereafter, every 10 minutes until the end of operation.

The colour and feel of the skin were noted throughout, together with the general condition and any response to surgical stimuli. Before extubation, the trachea, pharynx and mouth were aspirated.

Supplementary agents.

The only supplementary anaesthetic agent used was thiopentone. This was given towards the end of an operation if more relaxation was required, when it was undesirable to give more tubocurarine. It was needed in thirteen patients, eleven of whom were males. In all but two, the operation had taken over an hour and 50 mg of pecazine had been given. Thiopentone was injected in doses of 50 or 100 mg according to the patient, and no one had more than 200 mg.

RESULTS

Three deaths occurred within the first post-operative week. The earliest was 48 hours after operation. None of them could be attributed to anaesthesia.

Blood pressure and pulse.

Complete readings were obtained in over one hundred adults. Certain of the readings from the first hundred to be adequately recorded are shown in the accompanying chart (fig. 1). As the dosage

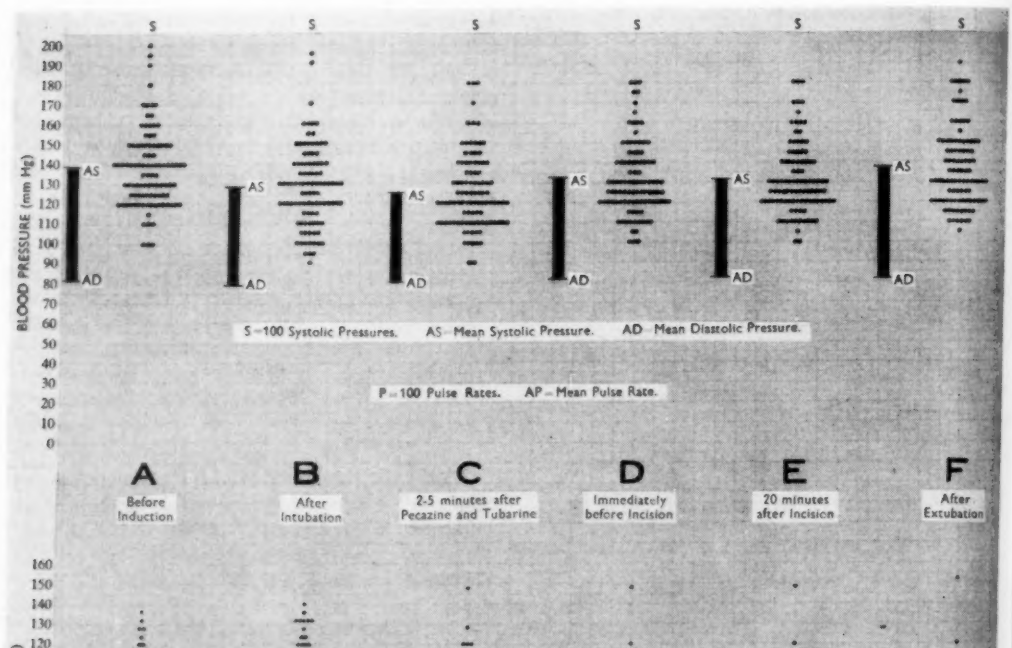


FIG. 1

of drugs was not the same in each case, and as the patients themselves varied in many respects, no statistical significance is claimed for these figures. They are included to convey a clinical impression. After thiopentone, suxamethonium and intubation, the blood pressure went down in the majority of cases. From the chart it can be seen that the average fall in systolic pressure was over 7 per cent. The pulse rate sometimes increased and sometimes slowed, the average being nearly the same, although individually it rarely remained so. Two to five minutes after giving the initial dose of pecazine and tubocurarine, i.e. about 10 minutes after the induction dose of thiopentone, the systolic pressure in most cases was a little lower, on the average 2 per cent. In only one case the pulse rate went up slightly (and remained up throughout operation). Most of the pulse rates were lowered; the average decrease was over 12 per cent, the higher rates falling more than the lower ones. Immediately before incision, i.e. about 10 minutes after the previous reading, the blood pressures were similar to those before induction, but the pulse rates remained lowered. During operation, subsequent increments of pecazine had little effect on the blood pressure, but sometimes caused slowing of the pulse further. If the heart rate is slowed too much, a fall in blood pressure may occur, as illustrated by the following case.

Case Record.

An otherwise fit young man, 28 years old, underwent an operation for cholecystectomy and exploration of the bile duct. His pulse rate at rest in bed was 48/minute and his blood pressure 120/80 mm Hg. For most of the anaesthetic the pulse rate was 40–44/minute and the blood pressure unchanged, but, after an hour, when pecazine 50 mg had been given the rate went down to 32/minute. Soon "coupling" of beats occurred and the blood pressure fell to 80/? mm Hg. By this time the peritoneum was being closed and atropine 0.65 mg was given intravenously, prior to administering neostigmine. The pulse rate went up to 52/minute immediately and the blood pressure returned to 120/80 mm Hg. There was no subsequent relapse.

It is relevant to mention another patient, aged 62, who behaved similarly, although not in this series.

Case Record.

This man was having an operation for ptosis. His pre-operative blood pressure was 135/80 mm Hg and pulse rate 68/minute. Pecazine 100 mg was given slowly intravenously before induction. Anaesthesia was induced with thiopentone 350 mg and suxamethonium 40 mg. After intubation anaesthesia was continued with nitrous oxide and oxygen, supplemented by minimal trichloroethylene. During the next 70 minutes the pulse rate and blood pressure fell gradually until the former was 52/minute, when the blood pressure dropped from 95/60 to 60/? mm Hg. Atropine 0.65 mg raised the pulse rate to 72/minute, and the blood pressure to 95/60 mm Hg within 2 minutes.

No other cardiac irregularities occurred in this series; but four elderly patients who had extrasystoles pre-operatively had regular pulses throughout operation.

Skin.

The skin was typically warm, dry and of good colour during anaesthesia. Usually, if sweating occurred, this was abolished by the next increment of pecazine. In eight cases, five of whom had raised temperatures on arrival, sweating persisted. In the author's experience this incidence rate is lower than that which occurs when nitrous oxide-oxygen-relaxant anaesthesia is used alone, or with pethidine or thiopentone as a supplement.

Bleeding.

Bleeding at the site of operation in many cases seemed to be increased. This took the form of a persistent ooze from cut surfaces, similar to that sometimes seen with cyclopropane. It is unlikely that carbon dioxide build-up occurred in any patient; with the technique used, the opposite is more probable. Presumably, with the doses given in this series, pecazine causes some vasodilatation with little or no lowering of the blood pressure and this results in oozing. Dobkin et al. (1957) have shown that chlorpromazine, another phenothiazine derivative, may prolong the prothrombin time, but whether pecazine behaves similarly is not known. It is only fair to state that no other author has noticed increased bleeding with larger doses of pecazine than have been used here. Déchêne states that there was a slight decrease in the average blood loss in one hundred cases of pulmonary resection. Williams (1957) says that, after pecazine, bleeding in tonsillectomy appeared to be reduced in amount.

Shock.

It seemed to the writer that there was a marked absence of "shock" in those cases where it might have been expected. Ill patients seemed much

better during the operation than they had done pre-operatively. They did not react unfavourably to surgical stimuli and gave the anaesthetist little or no cause for concern. As adequate blood replacement was always given if and when the need arose, the effect of severe blood loss was not ascertained.

Amount of relaxant required.

This did not seem to be affected by pecazine. The initial dosage of tubocurarine needed to produce complete respiratory paralysis, thus allowing effective controlled respiration, varied from 15 to 40 mg in adults. The average dose for a healthy male was 30 mg. There was no persistent curarization. The lungs were easy to inflate throughout anaesthesia and secretions were minimal.

Recovery.

Reflexes were present in all patients on leaving theatre. Within 15 minutes all but six patients opened their eyes when spoken to. Postoperative restlessness did not occur, however, and no patient received analgesics within 3 hours of operation.

Postoperative vomiting.

Seventy-nine cases had postoperative gastric suction. Of the remaining 156, seven vomited in the first 6 hours. In all, fourteen patients vomited once, six vomited two to four times, and four more frequently, in the 24 hours after operation. These last four were all rather obese women, three of whom had had cholecystectomies and the other an umbilical hernia repair. Vomiting was more frequent in females. Those cases who vomited once only, usually did so after taking their first fluid by mouth postoperatively, and six women said they had vomited after receiving an injection of morphine.

Other complications.

Two patients had painful thrombosis of the vein which had received the pecazine. All the other intravenous drugs had been given by the same vein. A "flare" along the line of the vein, similar to that seen sometimes with pethidine, was noted in twenty-four cases.

SUMMARY AND CONCLUSION

Pecazine was given intravenously to 235 patients during abdominal surgery, as a supplement to thiopentone-relaxant-oxygen-nitrous oxide anaesthesia. Small doses were used. The patients seemed to be protected from "shock", their blood pressure was little affected, their pulse rates were usually lowered and they looked well. Some troublesome oozing of blood from cut surfaces was noticed in several cases at operation. Two cases in which bradycardia was followed by hypotension are reported. They responded to atropine. Two cases of venous thrombosis occurred.

Postoperative recovery of consciousness was quick, but restlessness was absent. The incidence of postoperative vomiting was low.

In the author's opinion the use of pecazine in the manner described is a safe procedure and worthy of further trial.

REFERENCES

Davies, J. I., Huggins, D. H. M., and Wolkenstein, C. F. (1956). Pacatal in anaesthesia. *Canad. Anaesth. Soc. J.*, **3**, 224.

Déchêne, J. P. (1956). Pacatal in cardio-pulmonary surgery. *Laval méd.*, **21**, 1389.

Dobkin, A. B., Fisher, L. M., and Wyant, G. M. (1957). The effect of chlorpromazine on haemostasis. *Canad. Anaesth. Soc. J.*, **4**, 352.

Nieschulz, O., Popendiker, K., and Sack, K. (1954). Acute toxicity and comprehensive pharmacological report on Pacatal. *Arzneim. Mittel-Forsch*, **4**, 232.

Williams, H. (1957). Pacatal in anaesthesia. *N.Z. Med. J.*, **56**, 41.

Brit. J. Anaesth. (1958), **30**, 533

TREATMENT OF BARBITURATE POISONING*

BY

RAYMOND P. WISE

Department of Anaesthetics, Westminster Hospital, London

BARBITURATES vary in their speed of absorption and in their duration and intensity of effect. Their stability in vivo depends upon their chemical structure and there are two ways in which they can be eliminated by the body.

Short-acting compounds, such as quinalbarbitone, are rapidly and almost completely destroyed in the tissues, the liver being the main site of their degradation by a process of side chain oxidation.

The more stable barbiturates, such as barbitone, depend mainly on excretion through the kidneys for their elimination from the body.

The barbiturates in common use may be classified, as follows, according to their duration of action:

Long-acting:	Phenobarbitone Barbitone
Intermediate:	Butobarbitone Amylobarbitone
Short-acting:	Cyclobarbitone Quinalbarbitone Pentobarbitone Tuinal

They are produced in large and increasing quantities for medical use. The output in 1950 was about four times that in 1938 and the quantity prescribed in the general practitioner service has risen to almost fifty tons in a year.

Barbiturates are potentially dangerous drugs, because of their ability to produce habituation and addiction, but there seems little restriction on their extensive use in medical practice. In recent years the vast amounts of these drugs readily available to the public have resulted in a disquieting rise in the number of deaths from taking an overdose of them.

Figure 1 shows the annual deaths due to barbiturate poisoning from 1939 to 1956.

There has been, in the last 10 years especially, a marked rise in the number of suicidal deaths from barbiturate overdose and it must be emphasized that this has occurred without a concomitant rise in the suicide rate as a whole.

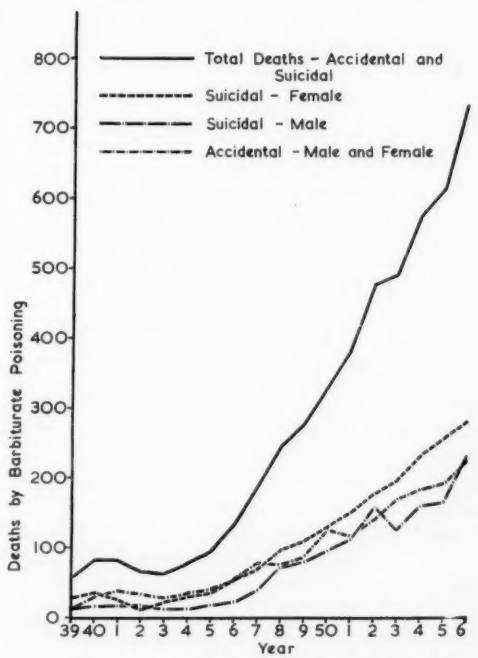


FIG. 1

Accidental, suicidal and total deaths by barbiturate poisoning, 1939–56. (*Registrar-General's Statistical Review of England and Wales.*)

* Essay awarded the May and Baker Registrars' Prize by the Royal Society of Medicine, May 1958.

The fatal dose of barbiturates is dependent upon many factors, but there is a serious risk to life after taking fifteen times the ordinary therapeutic dose.

BLOOD BARBITURATE LEVELS

These have been investigated by Broughton and others (1956), who showed that with the long-acting barbiturates the blood levels were higher and the rates of fall slower than those of the short-acting ones.

They found that the mean levels for the return of consciousness were:

Long-acting	7 mg/100 ml
Intermediate	3 mg/100 ml
Short-acting	1–2 mg/100 ml

As a qualitative test the estimation of blood barbiturate levels helps to elucidate the aetiology of undiagnosed cases of coma and, by serial estimations, it enables the clearance of the barbiturate from the blood to be followed.

Despite the development of this valuable technique, care must be exercised in interpreting the results.

Individual variation or the development of tolerance to the drug may influence the degree of depression produced at any given blood barbiturate level, as is demonstrated by figure 2. A chronic alcoholic regularly taking barbiturates was admitted in deep coma, having taken 6 grams of cyclobarbitone 12 hours beforehand, and was found to have a blood level of 10.0 mg/100 ml. In spite of this very high figure for a short-acting barbiturate, adequate ventilation was being maintained and there was no evidence of depression of the cardiovascular system. With the attainment of full consciousness 18 hours after admission the blood level was still 3 mg/100 ml.

In lethal doses the short-acting barbiturates, such as quinalbarbitone and pentobarbitone, produce a profound narcosis and death from respiratory paralysis within 20–30 minutes.

The longer-acting barbiturates result in a lower grade of narcosis, which is liable to terminate in bronchopneumonia.

METHODS OF TREATMENT

Analeptics.

During the 1930s reports were published on the action of nikethamide in antagonizing brome-

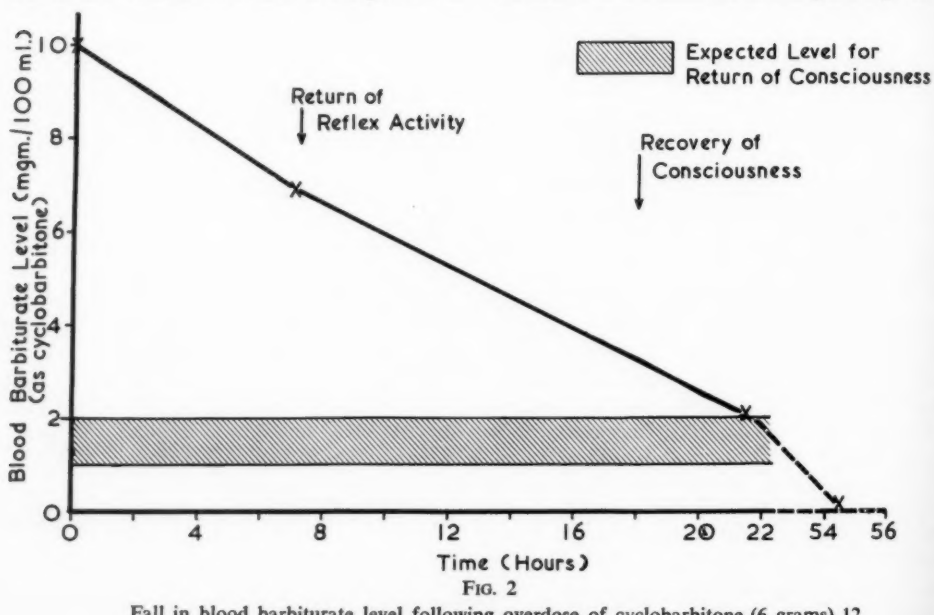


FIG. 2

Fall in blood barbiturate level following overdose of cyclobarbitone (6 grams) 12 hours before admission. (Female—60 years)

thol anaesthesia and the effects of a new convulsant drug, picrotoxin, were described by Maloney and others (1931).

In 1936 Grabfield recommended nikethamide and especially picrotoxin in the treatment of attempted suicide from barbiturate overdose. The repeated injections of large doses of analeptics became established as the most important factor in the treatment of barbiturate poisoning, with supporting measures playing a secondary role. The most commonly used drugs were picrotoxin, leptazol and nikethamide.

In spite of the widespread use of analeptics and the advantages claimed by the protagonists of this form of therapy, the mortality in severe cases remained at about 20 per cent during the period 1930–50. In 1945 Schmidt published the results of experiments performed on monkeys, anaesthetized with barbiturates. After the administration of convulsive doses of analeptics, he demonstrated a marked rise in cerebral blood flow and oxygen consumption, but this was followed by a prolonged period of depressed cerebral activity and oxygen uptake.

An analogous situation exists in the brain of a patient suffering from barbiturate poisoning, and it would be anticipated that the increased activity and oxygen requirements induced by the use of analeptics would lead to further cerebral depression. Of recent years the weight of opinion has been against their use, especially following the publication of a classic paper by Nilsson (1951). Using a conservative, nonstimulating type of treatment, he obtained a statistically significant improvement in the results of treatment over previously published figures, with a mortality rate of 2.3 per cent in a series of 176 cases.

The complications caused by the excessive use of analeptics include convulsions, vomiting (with an aspiration hazard) and cardiac arrhythmias. A deeply depressed patient can be kept alive only by the delivery of oxygen to his vital organs, especially the brain, and the failure of such cases to respond to analeptics is indicative of the extent to which the central nervous system is depressed.

Succinate.

The use of succinate was introduced following reports that brain tissue in vitro, depressed by barbiturates, could utilize succinate in its metabolism but not glucose, lactate and pyruvate.

The clinical and experimental results, however, have been disappointing, as usually improvement occurs only at light levels of narcosis (Wyke, 1957). Moreover, it has been shown that any effect produced is only indirectly due to the succinate, the immediate cause being changes in the ratio of ionized and un-ionized calcium in the blood, and this method of treatment has fallen largely into disuse.

Bemegride and Amiphenazole.

In 1954 Shulman and Shaw reported on the use of these two new barbiturate antagonists in reversing pentobarbitone narcosis in animals. Shulman and others (1955) subsequently reported on the treatment of barbiturate intoxication with these drugs in 41 cases, with one death.

In the treatment of barbiturate poisoning intravenous injections of bemegride and amiphenazole are made every few minutes until the so-called "safe" state is reached, as shown by the return of muscle tone and reflexes, together with voluntary movement and improvement in the blood pressure and respiration. The toxic signs of these drugs are vomiting, flickering of the fingers and finally convulsions, the e.e.g. showing the characteristic spikes of cerebral irritation.

The authors claim that, using this form of treatment, the immediate risk to life is minimized, complications ensuing from prolonged coma are reduced, and there is economy in the nursing care required in such cases.

Louw and Sonne (1956), in a series of 24 patients treated with bemegride, found it to have a marked effect on both respiration and reflex activity, but it did not influence the rate at which barbiturates were eliminated, the blood barbiturate level on waking, or the duration of coma. They concluded that the actions of bemegride could be explained more readily on the assumption of a central stimulant action, rather than action as a true biochemical antagonist of barbiturates.

Clemmesen (1956) treated 70 cases of barbiturate poisoning, including 7 with complete apnoea, and found that respiration recommenced and was restored to normal during or shortly after a course of bemegride and amiphenazole.

Case Record 1.

Figure 3 represents the course of a woman aged 59, who was admitted to hospital shortly after taking 8 grams of Tuinal. Tidal volume has been charted as a percentage of the optimal value, as calculated from the Radford nomogram (Radford et al., 1954) and a correction has also been made for the reduced dead-space due to the presence of an endotracheal tube.

Shortly after reaching hospital this patient became apnoeic, her pulse impalpable and blood pressure unrecordable. She was intubated with a cuffed endotracheal tube and her circulatory depression was combated effectively with 30 mg of methylamphetamine. Ventilation was maintained by using an intermittent positive pressure respirator adjusted to give her optimal tidal volume, as calculated from the nomogram.

Four hours after admission a course of bemegride 1.1 grams and amiphenazole 330 mg was administered over the course of 3½ hours. This failed to re-establish spontaneous respiration or, indeed, produce any evident response such as a return of reflexes or a rise of blood pressure. Fifteen hours after admission spontaneous respiration recommenced, but it was considered inadequate to prevent carbon dioxide accumulation and artificial respiration was continued until 27 hours after admission, when her tidal volume was 85 per cent of the optimal. A further course of bemegride and amiphenazole was given shortly after this, at a time when the level of narcosis was lightening, as shown by the return of spontaneous respiration and a cough reflex when tracheobronchial toilet was performed.

This course was accompanied by a rapid return of reflexes and a marked improvement in respiratory activity, the minute volume rising from 2.3 litres to 4.2 litres. The improvement shown in figure 3 is only 20 per cent, for a correction has been made for the hypothermia which existed before commencing the course of treatment. The temperature rose from 91° to 98°F over a period of 5½ hours, coinciding with the course of bemegride and amiphenazole and probably due to increased metabolism and a return of muscle tone.

The actual improvement in respiration accompanying such a rise in temperature obviously will not be as great as clinical observation or measurement of tidal volume would lead one to suppose, because of the increased metabolism which must be sustained at the higher temperature.

This sequence of events has been observed on several occasions when bemegride has been used in the presence of hypothermia and it may account in part for its reputation for improving respiration.

Case Record 2.

Figure 4 is a record of the progress of a man aged 35, admitted about 5 hours after taking 25 tablets of butobarbitone.

Gastric lavage was performed and he was intubated with a cuffed endotracheal tube, but the depth of coma increased and 4 hours later his tidal volume was only 50 per cent of the optimal, with evidence of carbon dioxide accumulation. Artificial respiration was com-

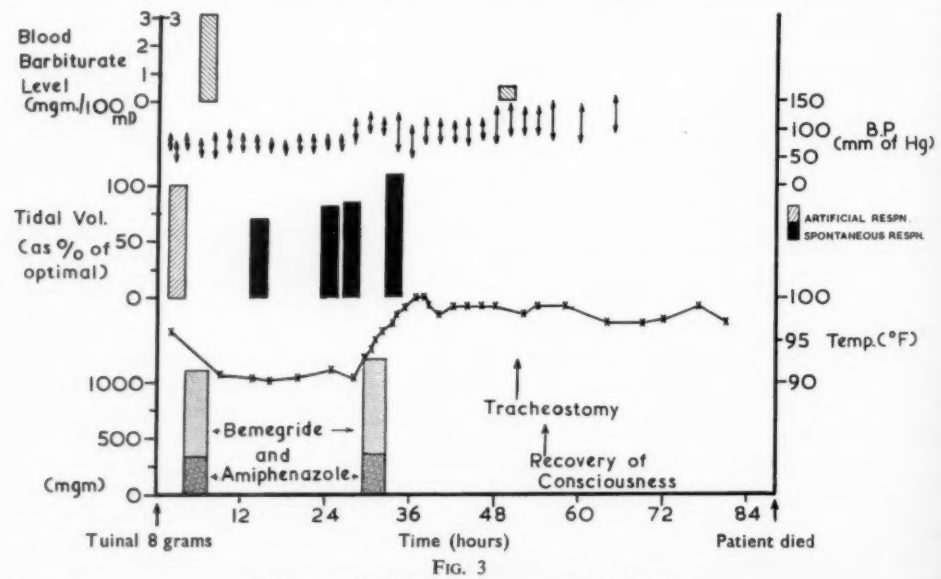


FIG. 3

Woman, aged 59, following overdose of Tuinal.

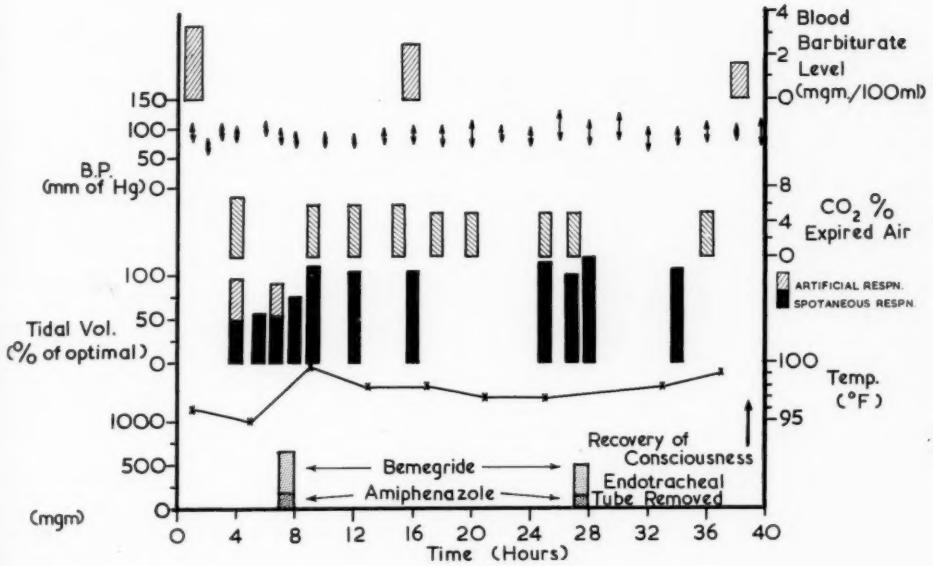


FIG. 4

Male, aged 35, following overdose of 25 tablets of butobarbitone.

menced with an intermittent positive pressure respirator adjusted to give his optimal tidal volume.

Following a course of bemegride 650 mg, and amiphenazole 195 mg, which had to be stopped because of the onset of generalized twitchings and tremors, the tidal volume rose by 50 per cent over a period of 2¼ hours.

This case also demonstrated a rise in temperature from 95° to 100°F during the course of treatment. Reflexes became hyperactive and he coughed when the endotracheal tube was disturbed.

Subsequently respiration remained adequate and the carbon dioxide percentage fell to normal limits.

A second course of bemegride and amiphenazole did not produce any alteration in his condition, and he recovered consciousness 39 hours after admission with a blood barbiturate level of 1.6 mg/100 ml.

It is difficult to assess the true position of bemegride in therapy, but from these reports it can be concluded that it is not the complete answer to the problem of barbiturate poisoning.

It does not appear to act as a true antagonist, but rather by a central stimulant action.

Little improvement can be anticipated when it is used in the presence of deep coma, for the results achieved seem to be inversely proportional to the degree of depression present.

It is a useful adjunct to other methods of treatment, especially for its stimulant action on respiration, but in severe barbiturate poisoning it can play only a subordinate role to the maintenance of an adequate blood pressure and respiratory exchange.

Physiological Methods.

General measures. The following scheme of treatment is based mainly on the methods of Plum and Swanson (1957), who have published the results of a series of 243 cases, with a mortality of 1.6 per cent.

Gastric lavage is performed on those patients who have taken the drug within the previous 6 hours. A cuffed endotracheal tube will guard against flooding of the tracheobronchial tree during this measure.

The patients are nursed on their side, with a head-down tilt, and are turned from side to side every 2 hours.

All patients in coma are placed on prophylactic penicillin therapy and the bladder is emptied periodically through an indwelling catheter.

Regular records are made of respiration, blood pressure, pulse, temperature, the reflexes present and urinary output

Patients in prolonged coma require parenteral fluid therapy and fluid balance is controlled by serial estimation of serum electrolytes.

Circulatory depression, with a fall in blood pressure to 80 mm Hg or less, is treated by injecting vasopressor agents such as ephedrine and methylamphetamine, while the more intractable cases may require phenylephrine, noradrenaline or even blood or dextran. Maintenance of the blood pressure at this level helps to sustain urinary secretion and also acts as a prophylaxis against cardiac arrhythmias.

Management of respiration. In the presence of respiratory obstruction which does not disappear with an oral airway, or in deep coma with absent laryngeal and pharyngeal reflexes, the patient is intubated with a cuffed endotracheal tube.

The mouth and pharynx are kept clear of mucus and saliva by frequent suction, while those cases with an endotracheal tube in situ must have tracheobronchial toilet performed when necessary, for secretions readily collect in the lower respiratory passages. Collapse of a lobe by a plug of mucus may necessitate bronchoscopy.

The value of artificial respiration has become increasingly recognized in the treatment of barbiturate poisoning for, in addition to complete apnoea, it may be required for shallow respiration. The assessment of its need, however, is made difficult by the reduced metabolism in the presence of hypothermia.

Measurement of the oxygen and carbon dioxide tensions in arterial blood would provide the answer, but is impracticable for general clinical use. A simpler way is to find the carbon dioxide tension of alveolar air, which ordinarily is the same as that of arterial blood. Samples of end expired air have a carbon dioxide tension close to that of alveolar air, but difficulty is experienced with this technique when respirations are shallow. Reventilation of expired air by the technique originally described by Plesch (1909) and more recently by Scurr (1956) gives consistent sampling values for carbon dioxide, which are of use in the assessment of ventilation.

Care is required in the use of oxygen therapy, for it does not aid the elimination of carbon dioxide and with a deeply depressed respiratory centre removal of the stimulus of hypoxia may result in complete apnoea.

Artificial respiration with intermittent positive pressure respirators and the indications for tracheostomy. In recent years tracheostomy has been performed on an increasing scale to provide a route through which artificial respiration can be provided for certain types of cases, including barbiturate poisoning, over a varying and often prolonged period (Nelson et al., 1957).

It is necessary to provide a clear airway and at the same time ready access to the tracheobronchial tree, so that accumulated secretions can be removed. Provision must also be made to guard against the ingress of salivary secretions and vomitus.

Initially these criteria can be met by a cuffed endotracheal tube, but the duration for which this can be left in situ is governed by the development of laryngeal oedema and ulceration of the cords and mucosa. The maximum safe period is thought to be about 48 hours. After this interval there is danger of complete respiratory obstruction from laryngeal oedema when the tube is removed.

Therefore, if the patient is still incapable of guarding his own airway after 48 hours, tracheostomy should be performed, although most cases will have attained adequate spontaneous respiration.

Briggs (1950), however, has reported a case in which an endotracheal tube was left in place for 42 days in a case of acute infectious polyneuritis. It must be emphasized that the percentage of barbiturate poisonings of such severity as to require tracheostomy and artificial respiration is very small.

The usual practice in America is to nurse the patient in a tank respirator. In this country, however, the use of an intermittent positive pressure respirator with a specially designed cuffed rubber tracheostomy tube has found more favour, the advantages being that the patient is readily accessible for nursing care, physiotherapy and frequent turning. The cuffed tube, moreover, provides an absolute barrier against the inhalation of material from the pharynx.

In order to ensure correct ventilation, more attention is being paid to the measurement of tidal volume with a spirometer or dry gas meter, and a nomogram (fig. 5) has been devised by Radford and others (1954) for estimating the expected optimal tidal volume for patients of different ages and weights, with correction for fever and the presence of a tracheostomy.

To assess spontaneous breathing, while artificial respiration is being employed, a period of apnoea must be permitted at regular intervals to allow sufficient carbon dioxide to accumulate to restart respiration. Use of the respirator is discontinued only when the tidal volume reaches the optimal level for the patient.

Positive pressure respirators, together with cabinet respirators, have the disadvantage that venous return is impaired during the inspiratory phase, resulting in a rise in central venous pressure and a fall in cardiac output. To counteract this undesirable tendency, inflation pressures should not be allowed to exceed 15–20 cm H_2O and the pressure curve should fall rapidly to that of the atmosphere at the end of each inflation of the lungs. The effect can be lessened by arranging a negative phase for part of the respiratory cycle, but in practice little advantage seems to accrue from having this additional refinement in the respirator.

Another complication arising from the use of a

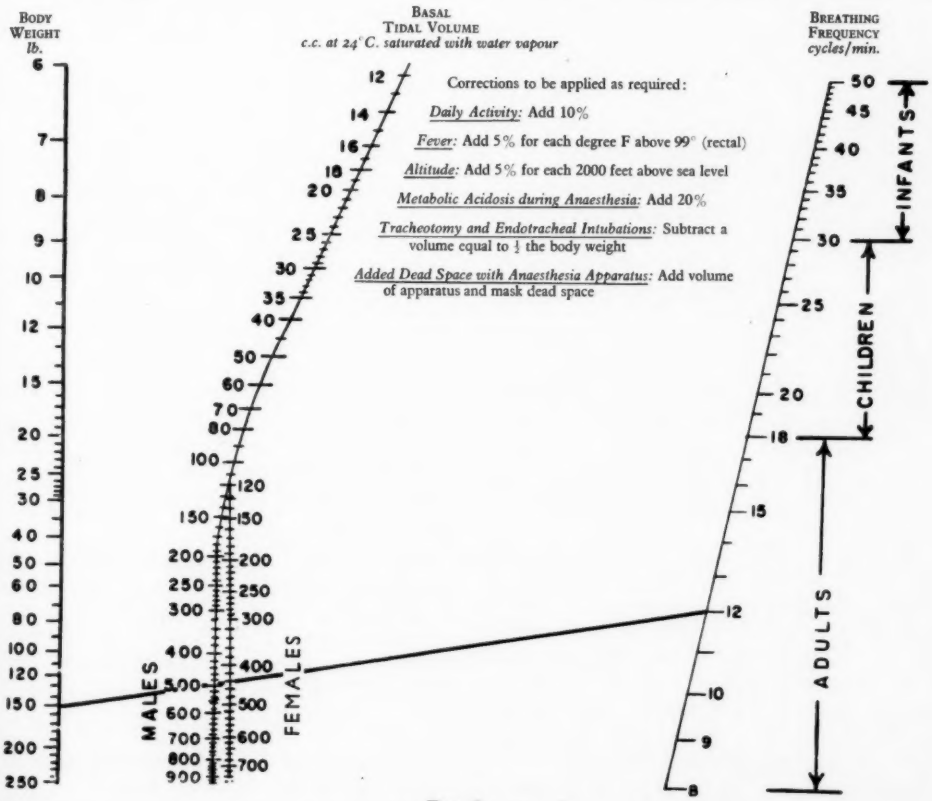

Body Weight lb.
Basal Tidal Volume c.c. at 24° C. saturated with water vapour
Breathing Frequency cycles/min.
Corrections to be applied as required:
Daily Activity: Add 10%
Fever: Add 5% for each degree F above 99° (rectal)
Altitude: Add 5% for each 2000 feet above sea level
Metabolic Acidosis during Anaesthesia: Add 20%
Tracheotomy and Endotracheal Intubations: Subtract a volume equal to ½ the body weight
Added Dead Space with Anaesthesia Apparatus: Add volume of apparatus and mask dead space
MALES
FEMALES
INFANTS
CHILDREN
ADULTS

FIG. 5

Nomogram for predicting the optimum tidal volume from the breathing frequency, body weight and sex of the patient.

(Reproduced by kind permission of the Authors and the Editor of the *New England Journal of Medicine*.)

positive pressure respirator is the occurrence of extreme drying and crusting of bronchial secretions, but this may be prevented by adequately humidifying the inspired air. Special emphasis must be placed on preventing blockage of the tracheostomy tube from encrustation or a plug of mucus. The patient previously mentioned (fig. 3), who had been brought from deep barbiturate coma to consciousness, died from this cause 60 hours after the cessation of intermittent positive pressure respiration.

Figure 6 is a photograph of an endotracheal tube which was left in position for about 24 hours

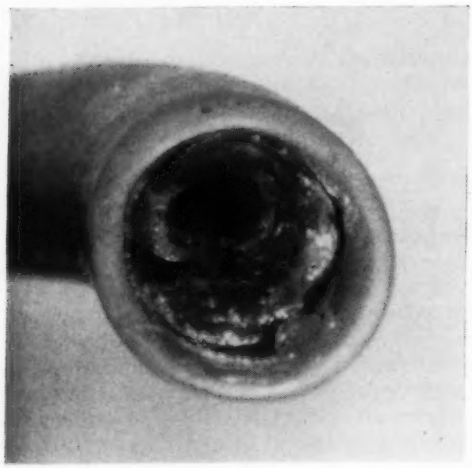


FIG. 6
Partial occlusion of the lumen of an endotracheal tube by dried, inspissated secretions.

postoperatively in a patient with a scabbard trachea and demonstrates the occlusion of its lumen by dried inspissated secretions. As can be seen, the occlusion was almost complete and the secretions had become so hard that they could not be removed by suction. An identical sequence of events and end result can occur when an endotracheal tube, or cuffed rubber tracheostomy tube, is used in cases of barbiturate poisoning.

Tracheobronchial toilet must be performed regularly and with the utmost thoroughness, especially after artificial respiration has been stopped and the air is no longer being humidified.

The replacement of the cuffed rubber tube by the more usual metal type, with a removal inner tube, is the most effective prophylaxis against excessive crust formation, but a certain interval must elapse before it can be certain that there is unlikely to be need for further artificial respiration.

During this period the inspired air may be humidified intermittently with Alevaire or even water by using a nebulizer. The vapour is delivered to the tracheostomy tube through a catheter.

Haemodialysis.

None of the methods so far described increases the rate of elimination of barbiturate from the body, yet this would appear to be the most rational approach to the treatment of this condition.

Using haemodialysis, 40 per cent of a dose of phenobarbitone in dogs can be recovered.

Berman and his colleagues (1956) have treated 8 cases of barbiturate poisoning by haemodialysis with an artificial kidney and have recovered up to 37 per cent of the dose of drug taken.

The rate of removal is dependent on the concentration gradient of barbiturate between the blood and the bath fluid. The greatest recovery is obtained, therefore, in deeply comatose patients with high blood barbiturate levels.

This procedure involves considerable technical difficulties and cannot be set up quickly. It cannot replace maintenance of respiration and the circulation, but it does pave the way for future developments in treatment, especially for prolonged coma due to long-acting barbiturates.

Electrical Stimulation.

Nonconvulsive electrical stimulation has been used since 1950 in cases of barbiturate poisoning to stimulate respiration and the circulation. Deeply comatose patients fail to respond to this measure and it is no substitute for the physiological methods previously advocated.

CONCLUSION

The results obtained in the treatment of cases of severe barbiturate poisoning depend in the ultimate analysis on the experience of the medical and nursing staff treating them. The principles of treatment are becoming more clearly defined, but

the number of cases seen annually in even a large hospital is limited.

The hour-to-hour medical supervision required is made difficult often by the calls of routine work and great reliance must be placed on the nursing staff, who need to have special experience of managing this type of case.

The physician, ear-nose-and-throat surgeon, and anaesthetist must work in close collaboration. The anaesthetist, by virtue of his special experience in the care of the air passages and maintenance of the failing circulation, has a very important part to play in therapy, but the ultimate responsibility for treatment rests with the physician.

In large centres of population the setting up of special units for treating cases of barbiturate poisoning, as has been done in Scandinavia, would help in reducing the mortality to the unavoidable minimum.

ACKNOWLEDGMENTS

I am indebted to Dr. G. S. W. Organe, at whose suggestion this paper was first written; to Dr. J. B. Wyman for his encouragement and helpful suggestions; to Dr. C. F. Scurr for his invaluable advice in the management of respiratory problems; to Dr. C. J. Gavey, Dr. S. P. Meadows and Dr. R. I. S. Bayliss for permission to quote details of patients admitted under their care; to Mr. B. T. Chatwick for estimating blood barbiturate levels; and to the staff of the Department of Medical Photography at Westminster Medical School for preparing the illustrations.

REFERENCES

Berman, L. B., Jeghers, H. J., Schreiner, G. E., and Pallotta, A. J. (1956). Haemodialysis: an effective therapy for acute barbiturate poisoning. *J. Amer. med. Ass.*, **161**, 820.

Briggs, B. (1950). Prolonged endotracheal intubation. *Anesthesiology*, **11**, 129.

Broughton, P. M. G., Higgins, G., and O'Brien, J. R. P. (1956). Acute barbiturate poisoning. *Lancet*, **1**, 180.

Clemmesen, C. (1956). Effect of megimide and amiphenazole on respiratory paresis. *Lancet*, **2**, 966.

Grabfield, G. P. (1936). The use of hypnotics. *J. Amer. med. Ass.*, **107**, 1381.

Louw, A., and Sonne, L. M. (1956). Megimide in the treatment of barbituric-acid poisoning. *Lancet*, **2**, 961.

Maloney, A. H., Fitch, R. H., and Tatum, A. L. (1931). Picrotoxin as an antidote in acute poisoning by shorter acting barbiturates. *J. Pharmacol*, **41**, 465.

Nelson, T. G., Pedigo, H. K., and Bowers, W. F. (1957). Use of tracheotomy in association with artificial and controlled respiration. *Anesthesiology*, **18**, 77.

Nilsson, E. (1951). On treatment of barbiturate poisoning: a modified clinical aspect. *Acta med. Scand., Suppl.* 253.

Plesch, J. (1909). Hämodynamische Studien. *Z. exp. Path. Ther.*, **6**, 380.

Plum, F., and Swanson, A. G. (1957). Barbiturate poisoning treated by physiological methods; with observations of effects of beta, beta-methylethylglutarimide and electrical stimulation. *J. Amer. med. Ass.*, **163**, 827.

Radford, E. P., Ferris, B. G., and Kriete, B. C. (1954). Clinical use of nomogram to estimate proper ventilation during artificial respiration. *New Engl. J. Med.*, **251**, 877.

Schmidt, C. (1945). Recent developments in respiratory physiology related to anaesthesia. *Anesthesiology*, **6**, 113.

Scurr, C. F. (1956). Pulmonary ventilation and carbon dioxide levels during anaesthesia. *Brit. J. Anaesth.*, **28**, 422.

Shaw, F. H., Simon, S. E., Cass, N., Shulman, A., Anstee, J. R., and Nelson, E. R. (1954). Barbiturate antagonism. *Nature, Lond.*, **174**, 402.

Shulman, A., Shaw, F. H., Cass, N. M., and Whyte, H. M. (1955). A new treatment of barbiturate intoxication. *Brit. med. J.*, **1**, 1238.

Wyke, B. D. (1957). Electrographic monitoring of anaesthesia. A method for experimental and clinical study of reversal of barbiturate narcosis. *Anaesthesia*, **12**, 373.

Brit. J. Anaesth. (1958), **30**, 542

A TRANSISTORIZED TIME MARKER

BY

DAVID ZUCK

Department of Anaesthesia, Chase Farm Hospital, Enfield, Middlesex

INTRODUCTION

THIS time marker was designed to work with a Nunn (1956) Continuous Flow Spirometer constructed in our department. A mechanical method was first considered, but experience with valve multivibrator timers over the past four years, in connection with the various models of the Enfield respirator, indicated that this was a reliable and trouble-free form of control, and the opportunity was taken to develop a transistorized device as a first step to transistorizing the respirator itself. The timer has now worked satisfactorily for some months, still powered by the original battery.

CONSTRUCTION

The timer is housed in a large plastic sandwich box with holes drilled for ventilation, and painted inside; the relay is mounted on the lid. Only two of the preset variable resistors which form the time controls are accessible from outside, the third—an afterthought to extend the time range—being inside the box.

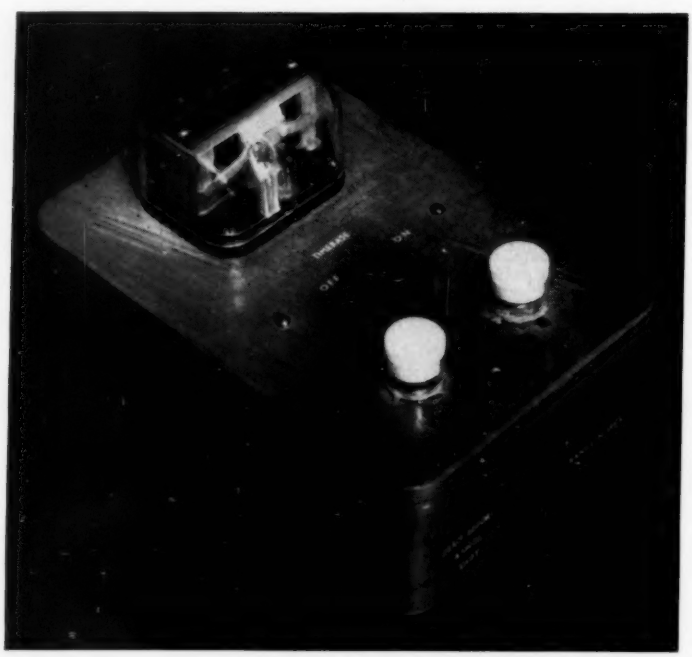


FIG. 1

"Red Spot" junction transistors have been used, but when other types which are freely available have been substituted they have been equally satisfactory. To avoid the dangers of soldering, the transistors may be mounted in "chocolate" connector or junction blocks, six sections being required. The values of the capacitor-resistor complexes can be varied within certain limits depending on the operating voltage; the values shown (fig. 2) are of components that happened to be available and have proved completely satisfactory for our purpose.

Sockets are provided for connection to the pen mechanism and, obscured in the photograph by the relay, for a bell-push; the latter enables an "incident" mark to be registered on the drum, when, for example, more thiopentone is injected, or the initial incision is made. The pen is a long hollow needle, swivel-mounted on a Type 3000 Post Office low resistance relay with the contacts removed. It is fed by a 5 ml syringe ink reservoir through a fine polythene tube, and actuated via the timer by 12 volts D.C. transformed and rectified mains current. A 4.5 volt bell battery is used to power the timer, and it is most important to connect it correctly.

CALIBRATION

The times chosen have been found most suitable for the drum speeds we commonly use in spirometry, and give 10 and 20 indications per minute. Other times can be set, of course, but the maximum interval is about 8 seconds at this voltage. To calibrate, the timer is switched on, and switch 2 is closed, short circuiting VR2. VR3 is then adjusted until a sufficiently short impulse is received by the pen relay to make a "spike" on the drum. VR1 is now rotated until these impulses recur at 3-second intervals; switch 2 is then opened, bringing VR2 into the circuit, and this

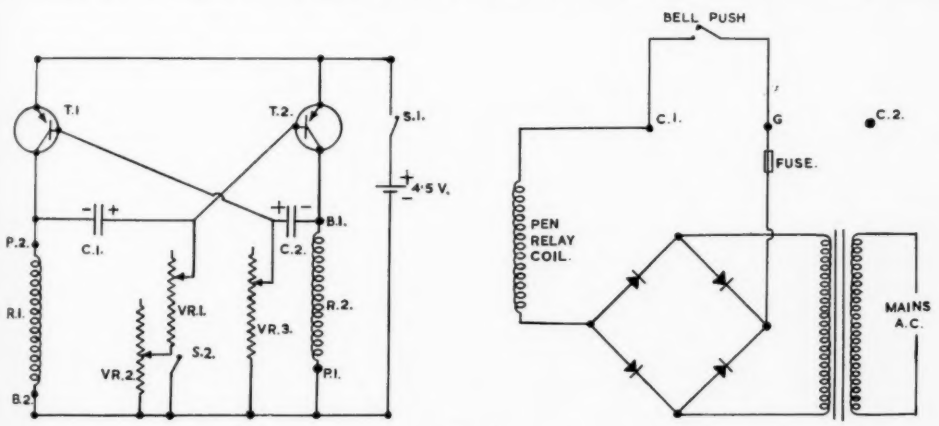


FIG. 2

Timer Circuit and Relay Contacts.

T1, T2 ..... "Red Spot", OC 71, or similar junction transistors.
C1 ..... Electrolytic capacitors in parallel to make 1500 mfd, 12 v.w.
C2 ..... Electrolytic, 500 mfd, 12 v.w.
VR1 ..... 5 K. preset variable resistor.
VR2 ..... 20 K. preset variable resistor.
VR3 ..... 3 K. preset variable resistor.
S1 and 2..... Single pole on-off switches.
4.5 volt bell battery.

R1 and R2 are the relay coils. The relay used is a "surplus" Barber-Colman Co. Micropositioner type AYLZ 2321, available from Proops Bros. of Tottenham Court Road, W.1.

The letters P1 B1, P2 B2 and C1 G C2 refer to terminal indications on the base of the micropositioner.

12 volts 1 amp. L.T. mains transformer and bridge rectifier. 1 amp. fuse and holder.

2 pairs plugs and sockets. Bell push.

is adjusted to give an impulse every 6 seconds. Once set, the timer is remarkably stable, and it is still dead accurate after the initial adjustment several months ago; but this has only been secured by protecting the controls from prying penknives, files, and idle fingers. This is achieved by cutting off the top half-inch of two plastic tablet tubes and cementing them over the preset spindles. Polythene caps are then inserted, and can be removed for adjustments if necessary. The box itself is sealed with sellotape.

OTHER APPLICATIONS

Within its limits the timer can be used as a repetitive switch for any kind of apparatus. It could, of course, be used as it stands to control solenoid valves in a respirator; but since it was made, a more advanced timer has been constructed using power transistors, and the coils R1 and R2 are now the solenoid coils of the gas valve itself. Apart from other improvements now introduced, there is considerable reduction of space and weight, and the total elimination of danger from sparks. It is hoped to publish this respirator circuit, which could be described as a mains-battery portable, when more fully tested.

ACKNOWLEDGMENTS

I must pay tribute to the mechanical skill of my colleague, Dr. P. W. S. Gray, who constructed the pen. I am also indebted to the North-East Metropolitan Regional Hospital Board for a research grant, and to Mr. S. E. Veronique of the Department of Medical Photography, Chase Farm Hospital, for the photograph of the timer.

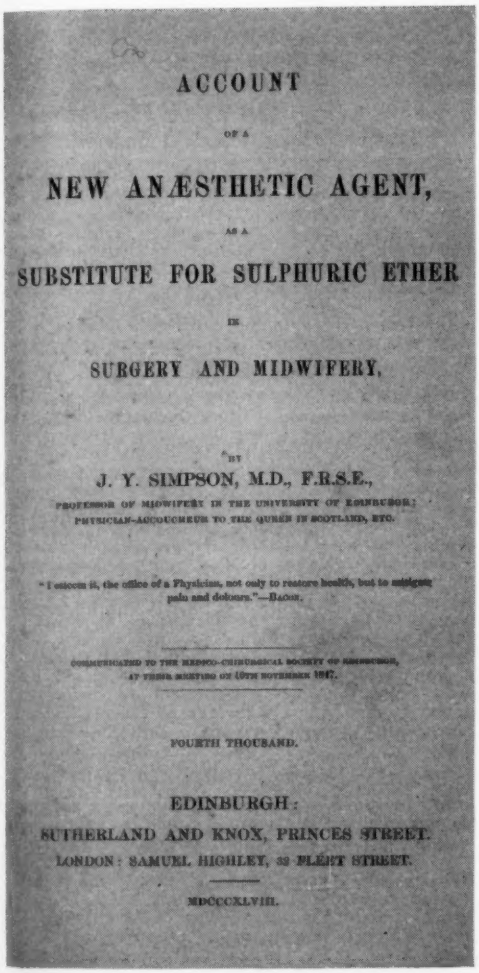
REFERENCE

Nunn, J. F. (1956). A new method of spirometry applicable to routine anaesthesia. *Brit. J. Anaesth.*, **28**, 440.

NEW ANAESTHETIC AGENT AS A SUBSTITUTE FOR SULPHURIC ETHER IN SURGERY AND MIDWIFERY

BY

J. Y. SIMPSON



ACCOUNT

OF A

NEW ANÆSTHETIC AGENT,

AS A

SUBSTITUTE FOR SULPHURIC ETHER

IN

SURGERY AND MIDWIFERY,

BY

J. Y. SIMPSON, M.D., F.R.S.E.,

PROFESSOR OF MIDWIFERY IN THE UNIVERSITY OF EDINBURGH;
PHYSICIAN-ACCOUCHEUR TO THE QUEEN IN SCOTLAND, ETC.

"I esteem it, the office of a Physician, not only to restore health, but to mitigate pain and dolours."—BACON.

COMMUNICATED TO THE MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH, AT THEIR MEETING ON 10TH NOVEMBER 1847.

FOURTH THOUSAND.

EDINBURGH:
SUTHERLAND AND KNOX, PRINCES STREET.
LONDON: SAMUEL HIGHLEY, 32 FLEET STREET.

MDCCCXLVIII.

Facsimile of the original title page.

ON CHLOROFORM

From the time at which I first saw Ether-Inhalation successfully practised in January last, I have had the conviction impressed upon my mind, that we would ultimately find that other therapeutic agents were capable of being introduced with equal rapidity and success into the system, through the same extensive and powerful channel of pulmonary absorption. In some observations, which I wrote and published in February last, relative to the inhalation of sulphuric ether in midwifery, I stated that, in several obstetric cases, I had used ergot of rye in this way, along with ether.—(See *Monthly Journal of Medical Science*, pp. 724; and 795, case of successful inhalation of opium, to arrest the vomiting of pregnancy.)

With various professional friends, more conversant with chemistry than I am, I have, since that time, taken opportunities of talking over the idea which I entertained of the probable existence or discovery of new therapeutic agents, capable of being introduced into the system by respiration, and the possibility of producing for inhalation vaporizable or volatile preparations of some of our more active and old established medicines: and I have had, during the summer and autumn, ethereal tinctures, &c., of several potent drugs, manufactured for me, for experiment, by Messrs Duncan, Flockhart, & Co., the excellent chemists and druggists of this city.

Latterly, in order to avoid, if possible, some of the inconveniences and objections pertaining to sulphuric ether,—(particularly its disagreeable and very persistent smell, its occasional tendency to irritation of the bronchi during its first inspirations, and the large quantity of it occasionally required to be used, more especially in protracted cases of labour,)—I have tried upon myself and others the inhalation of different other volatile

fluids, with the hope that some one of them might be found to possess the advantages of ether, without its disadvantages. For this purpose, I selected for experiment and have inhaled several chemical liquids of a more fragrant or agreeable odour, such as the chloride of hydro-carbon (or Dutch liquid), acetone, nitrate of oxide of ethyle (nitric ether), benzin, the vapour of iodoform, &c.* I have found, however, one infinitely more efficacious than any of the others, viz., Chloroform, or the Perchloride of Formyle, and I am enabled to speak most confidently of its superior anaesthetic properties, having now tried it upon upwards of thirty individuals. The liquid I have used has been manufactured for me by Mr Hunter, in the laboratory of Messrs Duncan, Flockhart, & Co.

Chloroform was first discovered and described at nearly the same time by Soubeiran (1831), and Liebig, (1832); its composition was first accurately ascertained by the distinguished French chemist, Dumas, in 1835.—See the *Annales de Chimie et de Physique*, vols. xlviii. xlix. and lviii. It has been used by some practitioners internally; Guillot prescribed it as an anti-spasmodic in asthma, exhibiting it in small doses, and diluted 100 times. —(See Bouchardat's *Annuaire de Therapeutique* for 1844, p. 35.) But no person, so far as I am aware, has used it by inhalation, or discovered its remarkable anæsthetic properties till the date of my own experiments.

It is a dense, limpid, colourless liquid, readily evaporating, and possessing an agreeable, fragrant, fruit-like odour, and a saccharine pleasant taste.

As an inhaled anæsthetic agent, it possesses over sulphuric Ether the following advantages:—

1. A greatly less quantity of Chloroform than of Ether is requisite to produce the anæsthetic effect; usually from a hundred to a hundred and twenty drops of Chloroform only being sufficient; and with some patients much less. I have seen a strong person rendered completely insensible by six or seven inspirations of thirty drops of the liquid.

2. Its action is much more rapid and complete, and generally more persistent. I have almost always seen from ten to twenty full inspirations suffice. Hence the time of the surgeon is saved; and that preliminary stage of excitement, which pertains to all narcotizing agents, being curtailed, or indeed practically abolished, the patient has not the same degree of tendency to exhilaration and talking.†

3. Most of those who know from previous experience the sensations produced by ether inhala-

* In talking over, with different chemists, what fluids might be sufficiently volatile to be respirable, and hence deserving of being experimented upon, Mr Waldie first named to me the Perchloride of Formyle as worthy, among others, of a trial;—Dr Gregory suggested a trial of the chloride of hydrocarbon, &c. I have been deeply indebted to Dr Gregory and Dr. Anderson, for their kindness in furnishing me with the requisite chemical agents for these experiments;—and also to my assistants, Dr Keith and Dr Duncan, for the great and hearty zeal with which they have constantly aided me in conducting the inquiry.

† In practice I have found that any such tendency, even with ether, is avoided by, 1st, giving the patient from the first a large and overwhelming dose of the vapour, and 2ndly, by keeping him perfectly quiet and still, and preventing all noise and talking around him. I have elsewhere insisted on the importance of these points. (See the numbers of the Monthly *Journal of Medical Science* for March, 1847, p. 726, and for September, p. 154). In the paper last referred to, I took occasion, when discussing the conditions requisite for insuring successful etherization, to observe, "*First*, The patient ought to be left, as far as possible, in a state of absolute quietude and freedom from mental excitement, both during the induction of etherization, and during his recovery from it. All talking and all questioning should be strictly prohibited. In this way any tendency to excitement is eschewed, and the proper effect of the ether inhalation more speedily and certainly induced. And, *Secondly*, with the same view, the primary stage of exhilaration should be entirely avoided, or at least reduced to the shortest possible limit, by impregnating the respired air as fully with the ether vapour as the patient can bear, and by allowing it to pass into the lungs both by the mouth and nostrils, so as rapidly and at once to superinduce its complete and anæsthetic effect; * * * * a very common but certainly a very unpardonable error being to exhibit an imperfect and exciting, instead of a perfect and narcotizing dose of the vapour. Many of the alleged failures and misadventures are doubtless entirely attributable to the neglect of this simple rule;—not the principle of etherization, but the mode of putting it in practice being altogether to blame. But, *Thirdly*, whatever means or mode of etherization is adopted, the most important of the conditions required for procuring a satisfactory and successful result from its employment in surgery, consists in obstinately determining to avoid the commencement of the operation itself, and never venturing to apply the knife *until* the patient is under the full influence of the ether-vapour, and *thoroughly and indubitably soporized by it*." In fulfilling all these indications, the employment of Chloroform evidently offers great and decided advantages, in facility and efficiency, over the employment of Ether.

tion, and who have subsequently breathed the Chloroform, have strongly declared the inhalation and influence of Chloroform to be far more agreeable and pleasant than those of Ether.

4. I believe, that considering the small quantity requisite, as compared with Ether, the use of Chloroform will be less expensive than that of Ether; more especially, as there is every prospect that the means of forming it may be simplified and cheapened.

5. Its perfume is not unpleasant, but the reverse; and the odour of it does not remain, for any length of time, obstinately attached to the clothes of the attendant,—or exhaling in a disagreeable form from the lungs of the patient, as so generally happens with Sulphuric Ether.

6. Being required in much less quantity, it is much more portable and transmissible than Sulphuric Ether.

7. No special kind of inhaler or instrument is necessary for its exhibition. A little of the liquid diffused upon the interior of a hollow-shaped sponge, or a pocket-handkerchief, or a piece of linen or paper, and held over the mouth and nostrils, so as to be fully inhaled, generally suffices in about a minute or two to produce the desired effect.*

I have not yet had an opportunity of using Chloroform in any capital surgical operation, but have exhibited it with perfect success, in tooth-drawing,† opening abscesses, for annulling the pain of dysmenorrhœa and of neuralgia, and in two or three cases where I was using deep, and otherwise very painful galvano-puncture for the treatment of ovarian dropsy, &c. I have employed it also in obstetric practice with entire success. The lady to whom it was first exhibited during parturition, had been previously delivered in the country by perforation of the head of the infant, after a labour of three days' duration. In this, her second confinement, pains supervened a fortnight before the full time. Three hours and a-half after they commenced, and, ere the first stage of the labour was completed, I placed her under the influence of the Chloroform, by moistening, with half a tea-spoonful of the liquid, a pocket handkerchief, rolled up into a funnel shape, and with the broad or open end of the funnel placed over her mouth and nostrils. In consequence of the evaporation of the fluid, it was once more renewed in about ten or twelve minutes. The child was expelled in about twenty-five minutes after the inhalation was begun. The mother subsequently remained longer soporose than commonly happens after Ether. The squalling of the child did not, as usual, rouse her; and some minutes elapsed after the placenta was expelled, and after the child was removed by the nurse into another room, before the patient awoke. She then turned round and observed to me that she had "enjoyed a very comfortable sleep, and indeed required it, as she was so tired,‡ but would now be more able for the work before her." I evaded entering into conversation with her, believing, as I have already stated, that the most complete possible quietude

* When used for surgical purposes, perhaps it will be found to be most easily given upon a handkerchief, gathered up into a cup-like form in the hand of the exhibitor, and with the open end of the cup placed over the nose and mouth of the patient. For the first inspiration or two, it should be held at the distance of half an inch or so from the face, and then more and more closely applied to it. To insure a rapid and perfect anæsthetic effect—more especially where the operation is too severe—one or two teaspoonfuls of the Chloroform should be at once placed upon the hollow of the handkerchief, and immediately held to the face of the patient. Generally a snoring sleep speedily supervenes; and when it does so, it is a perfect test of the superinduction of complete insensibility. But a patient may be quite anæsthetic without this symptom supervening.

† A young dentist who has himself had two teeth extracted lately,—one under the influence of Ether, and the other under the influence of Chloroform,—writes me the following statement of the results:—"About six months ago I had an upper molar tooth extracted whilst under the influence of Ether, by Mr Imlach. The inhalation was continued for several minutes before I presented the usual appearance of complete etherization; the tooth was then extracted; and, although I did not feel the least pain, yet I was conscious of the operation being performed, and was quite aware when the crash took place. Some days ago I required another molar extracted on account of tooth-ache, and this operation was again performed by the same gentleman. I inhaled the vapour of Chloroform, half a drachm being poured upon a handkerchief for that purpose, and held to my nose and mouth. Insensibility took place in a few seconds; but I was so completely *dead* this time, that I was not in the very slightest degree aware of any thing that took place. The subsequent stupifying effects of the Chloroform went off more rapidly than those of the Ether; and I was perfectly well and able again for my work in a few minutes."

‡ In consequence of extreme anxiety at the unfortunate result of her previous confinement, she had slept little or none for one or two nights preceding the commencement of her present accouchement.

forms one of the principal secrets for the successful employment of either Ether or Chloroform. In a little time she again remarked that she was afraid her "sleep had stopped the pains." Shortly afterwards, her infant was brought in by the nurse from the adjoining room, and it was a matter of no small difficulty to convince the astonished mother that the labour was entirely over, and that the child presented to her was really her "own living baby."

Perhaps I may be excused from adding, that since publishing on the subject of Ether Inhalation in Midwifery, seven or eight months ago,* and then for the first time directing the attention of the medical profession to its great use and importance in natural and morbid parturition, I have employed it, with few and rare exceptions, in every case of labour that I have attended; and with the most delightful results. And I have no doubt whatever, that some years hence the practice will be general. Obstetricians may oppose it, but I believe our patients themselves will force the use of it upon the profession.† I have never had the pleasure of watching over a series of better and more rapid recoveries; nor once witnessed any disagreeable result follow to either mother or child; whilst I have now seen an immense amount of maternal pain and agony saved by its employment. And I most conscientiously believe that the proud mission of the physician is distinctly two-fold—namely, to alleviate human suffering, as well as preserve human life.

CHEMICAL CONSTITUTION OF CHLOROFORM.

Formyle is the hypothetical radical of Formic acid. In the red ant (*Formica rufa*) formic acid was first discovered, and hence its name. Gehlen pointed it out as a peculiar acid; and it was afterwards first artificially prepared by Doebereiner. Chemists have now devised a variety of processes, by which formic acid may be obtained from starch, sugar, and, indeed, most other vegetable substances.

A series of Chlorides of Formyle are produced when chlorine and the hypochlorites are brought to act on the chloride, oxide, and hydrated oxide of methyle, (pyroxylic or wood spirit). In the same way as formic acid may be artificially procured from substances which do not contain Formyle ready formed,—so also are the Chlorides of this radical capable of being procured from substances which do not originally contain it.

Chloroform, Chloroformyle, or the Perchloride of Formyle, may be made and obtained artificially by various processes,—as by making milk of lime, or an aqueous solution of caustic alkali act upon chloral,—by distilling alcohol, pyroxylic spirit, or acetone, with chloride of lime,—by leading a stream of chlorine gas into a solution of caustic potass in spirit of wine, &c. The preparation which I have employed, was made according to the following formula of Dumas:—

"℞ Chloride of lime in powder, . . . lb. IV.
Water, ... lb. XII.
Rectified Spirit, ... f ℥XII.

"Mix in a capacious retort or still, and distil as long as a dense liquid, which sinks in the water with which it comes over, is produced."—(Gray's *Supplement to the Pharmacopœia*, 1846, p. 633).

The resulting Perchloride of Formyle consists of two atoms of Carbon, one of Hydrogen, and three of Chlorine. Its specific gravity is much greater than that of water, being as high as 1·480. It boils at 141°. The density of its vapour is 4·2. It is not inflammable; nor changed by distillation with potassium, potash, sulphuric, or other acids. —(See Turner's *Elements of Chemistry*, 8th edition, p. 1009; Gregory's *Outlines of Chemistry*, part ii. p. 401; Fownes' *Manual of Elementary Chemistry*, p. 419; Thomson's *Chemistry of Organic Bodies*, p. 312; Loewig's *Organische Chemie*, vol. i. p. 498).

It is now well ascertained that three compound chemical bodies possess, when inhaled into the lungs, the power of superinducing a state of anæsthesia, or insensibility to pain in surgical operations, &c., namely, Nitrous Oxide, Sulphuric Ether, and Perchloride of Formyle. The following tabular view shows that these agents are entirely different from each other in their chemical constitution, and hence that their elementary composition affords no apparent clue to the explanation of their anæsthetic properties:—

* See *Monthly Journal of Medical Science* for February, p. 639; for March, p. 718 and 721; and April, p. 794, &c.

† I am told that the London physicians, with two or three exceptions only, have never yet employed ether-inhalation in their Midwifery practice. Three weeks ago, I was informed in a letter from Professor Montgomery of Dublin, that he believed that in that city, up to that date, it had not been used in a single case of labour.

	Propor. of Nitrogen.	Propor. of Oxygen.	Propor. of Carbon.	Propor. of Hydrogen.	Propor. of Chlorine.
Nitrous Oxide,	1 Atom.	1 Atom.	...	...	...
Sulphuric Ether,	...	1 Atom.	4 Atoms.	5 Atoms.	...
Chloroform,	...	...	2 Atoms.	1 Atom.	3 Atoms.

It is perhaps not unworthy of remark, that when Soubeiran, Liebig, and Dumas engaged, a few years back, in those inquiries and experiments by which the formation and composition of Chloroform was first discovered, their sole and only object was the investigation of a point in philosophical Chemistry. They laboured for the pure love and extension of knowledge. They had no idea that the substance to which they called the attention of their chemical brethren could or would be turned to any *practical* purpose, or that it possessed any physiological or therapeutic effects upon the animal economy. I mention this to show, that the *cui bono* argument against philosophical investigations, on the ground that there may be at first no apparent practical benefit to be derived from them, has been amply refuted in this, as it has been in many other instances. For I feel assured, that the use of Chloroform will soon entirely supersede the use of Ether; and, from the facility and rapidity of its exhibition, it will be employed as an anæsthetic agent in many cases, and under many circumstances, in which Ether would never have been had recourse to. Here then we have a substance which, in the first instance, was merely interesting as a matter of scientific curiosity and research, becoming rapidly an object of intense importance, as an agent by which human suffering and agony may be annulled and abolished, under some of the most trying circumstances in which human nature is ever placed.

POSTSCRIPT

Since the above observations were sent to the press, I have—through the great kindness of Professor Miller and Dr Duncan—had an opportunity of trying the effects of the inhalation of Chloroform, to-day, in three cases of operation in the Royal Infirmary of Edinburgh. A great collection of professional gentlemen and students witnessed the results, and among the number was Professor Dumas of Paris, the chemist who first ascertained and established the chemical composition of Chloroform. He happened to be passing through Edinburgh, engaged along with Dr Milne Edwards, who accompanied him, in an official investigation for the French Government,—and was, in no small degree, rejoiced to witness the wonderful physiological effects of a substance with whose chemical history his own name was so intimately connected.

I append notes, obligingly furnished to me by Professor Miller and Dr Duncan, of the three cases of operation. The two first cases were operated on by Professor Miller; the third by Dr Duncan. In applying the Chloroform in the first case, I used a pocket-handkerchief as the inhaling instrument; in the two last I employed a hollow sponge.

CASE I.—" A boy, four or five years old, with necrosis of one of the bones of the fore-arm. Could speak nothing but Gaelic. No means, consequently, of explaining to him what he was required to do. On holding a handkerchief, on which some Chloroform had been sprinkled, to his face, he became frightened, and wrestled to be away. He was held gently, however, by Dr Simpson, and obliged to inhale. After a few inspirations he ceased to cry or move, and fell into a sound snoring sleep. A deep incision was now made down to the diseased bone; and, by the use of the forceps, nearly the whole of the radius, in the state of sequestrum, was extracted. During this operation, and the subsequent examination of the wound by the finger, not the slightest evidence of the suffering of pain was given. He still slept on soundly, and was carried back to his ward in that state. Half an hour afterwards, he was found in bed, like a child newly awakened from a refreshing sleep, with a clear merry eye, and placid expression of countenance, wholly unlike

what is found to obtain after ordinary etherization. On being questioned by a Gaelic interpreter who was found among the students, he stated that he had never felt any pain, and that he felt none now. On being shown his wounded arm, he looked much surprised, but neither cried nor otherwise expressed the slightest alarm."

CASE II.—"A soldier who had an opening in the cheek—the result of exfoliation of the jaw—was next made to inhale. At first he showed some signs of moving his hands too freely; but soon also fell into a state of sleep and snoring. A free incision was made across the lower jaw, and from this the dense adhering integuments were freely dissected all round, so as to raise the soft parts of the cheek. The edges of the opening were then made raw, and the whole line of incision was brought together by several points of suture. This patient had previously undergone two minor operations of a somewhat similar kind; both of them had proved unsuccessful, and he bore them very ill—proving unusually unsteady, and complaining bitterly of severe pain. On the present occasion, he did not wince or moan in the slightest degree; and, on the return of consciousness, said that he had felt nothing. His first act, when apparently about half awake, was suddenly to clutch up the sponge with which the Chloroform was used, and re-adjust it to his mouth, obviously implying that he had found the inhalation from it anything but a disagreeable duty.

"This case was further interesting as being one of those operations in the region of the mouth, in which it has been deemed impossible to use ether,—and certainly it would have been impossible to have performed the operation with any complicated inhaling apparatus applied to the mouth of the patient."

CASE III.—"A young man, of about twenty-two years of age, having necrosis of the first phalanx of the great toe, and ulceration of the integuments, the consequence of injury. The ulcerated surface was exceedingly tender to the touch—so much so, that he winced whenever the finger was brought near to it; and the slightest pressure made him cry out. After the removal of the dressings, which caused some pain and fretting, the inhalation was commenced, and the patient almost immediately* became insensible, and lay perfectly still, while the diseased mass was being removed by amputation of the toe through the middle of the second phalanx. The inhalation was now stopped. The edges of the wound were then brought together with three stitches, and the wound dressed. The patient shortly afterwards awoke, looked round him, and gratefully declared his entire and perfect freedom from all pain and uneasiness during the operation."

The whole quantity of Chloroform used in these three operations did not exceed half an ounce,—and, as Professor Miller afterwards observed to the students that were present, if ether had been used, several ounces of it would have been requisite to produce the same amount of anæsthetic effect.

The following case occurred also to-day, to Mr Miller, in private practice. The notes of it and the subsequent remark are in his own words.

CASE IV.—"A young lady wished to have a tumour (encysted) dissected out from beneath the angle of the jaw. The Chloroform was used in small quantity (about a drachm), sprinkled upon a piece of operation sponge. In considerably less than a minute she was sound asleep, sitting easily in a chair, with her eyes shut, and with her ordinary expression of countenance. The tumour was extirpated, and a stitch inserted, without any pain having been either shown or felt. Her sensations, throughout, as she subsequently stated, had been of the most pleasing nature; and her manageableness during the operation was as perfect as if she had been a wax doll or a lay figure.

"No sickness, vomiting, headache, salivation, uneasiness of chest, in any of the cases. Once or twice a tickling cough took place in the first breathings."

I have, up to this date, exhibited the Chloroform to about fifty individuals. In not a single instance has the slightest bad result of any kind whatever occurred from its employment.

EDINBURGH, 15*th November* 1847.

* Dr Christison, who was watching the result, informs me that this patient was affected in half a minute.

FINIS.

CORRESPONDENCE

ACCIDENTAL INTRA-ARTERIAL ADMINISTRATION OF THIOPENTONE ON THE BACK OF THE HAND

Sir,—It is possible that the explanation Dr. Baillie offers for the events noted in his Case 1 (Baillie, 1958) is correct.

I feel, however, that he has noticed a phenomenon which has been commonly recognized here for at least five years. The injection of the thiopentone is in fact made accurately intravenously, in a vein on the dorsum of the hand, the volar surface of the wrist, or the dorsum of the foot. The weather is usually cold, and the peripheral circulation poor. It is typically seen in young women who lead inactive lives, although anyone may show it.

Immediately after the injection has begun, the patient complains of severe pain, as described by Dr. Baillie. Blanching of the skin occurs in a patchy distribution over an area both distal and proximal to the needle point. The intensity of the pain and blanching is related to the pressure of the injection, and very slow injection allows the drug to be given painlessly. On several occasions, at the site of blanching, oedema of the skin has been noted subsequently, and, once, a localized superficial necrosis of the skin followed.

Possibly in these cases, the thiopentone goes more readily into the area normally drained by the vein than into the larger veins of the limb, probably owing to absence of valves. The injected fluid passes from the capillaries into the tissue spaces and so produces a local response to injury.

After the normal vasodilatation of anaesthesia begins, the phenomenon does not recur. No treatment is necessary.

Use of 2½ per cent thiopentone does not alter its occurrence.

J. H. STACE
Hyde Park, South Australia

REFERENCE

Baillie, T. W. (1958). Accidental intra-arterial administration of thiopentone on the back of the hand. *Brit. J. Anaesth.*, **30**, 373.

FILM REVIEW

Atrial Septal Defect. A 16-mm colour film, made at the Middlesex Hospital, London, in 1958. Running time 35 minutes.

The film opens with an "animated" sequence describing the anatomical types of atrial septal defect. The diagnostic signs and symptoms are listed and illustrated with radiographs, electrocardiograms and cardiac catheterization findings from a 17-year-old girl. The film then records the anaesthetic and surgical management of this patient. Premedication, induction and the technique of hypothermia are shown in detail, followed by the filming of the important parts of the surgical closure of the defect through the open right atrium during circulatory arrest at 30°C. Surface rewarming and the return to the ward conclude this sequence. The smooth postoperative course is indicated from the patient's hospital chart. The film ends with the cardiologist's interview with the patient three months postoperatively, when she is told that she may now lead a perfectly normal life.

The film clearly demonstrates the excellent teamwork between cardiologists (Drs. Evan Bedford and W. Somerville), surgeon (Mr. Holmes Sellors) and anaesthetist (Dr. B. Sellick). In the unhurried and smooth management of the anaesthesia and operation the film suggests the good results obtained at the Middlesex Hospital in now well over 100 cases of atrial septal defect similarly treated.

This excellently arranged and produced film has been made for showing primarily to general practitioners and other nonspecialists. However, anaesthetists will find it interesting and instructive.

Ronald Woolmer

BOOK REVIEW

Narkose-Fibel. By H. J. Thum. Published by Georg Thieme Verlag, Stuttgart. Pp. viii + 103; 10 figs.

Dr. Thum presents an elementary but concise and comprehensive summary of the field of anaesthesia. Intended for the anaesthetist's assistants rather than himself, it is sure to provide them with a ready source of explanation of unfamiliar terminology or ideas. Illustrations are conspicuous by their virtual absence, but no doubt by their omission the size and the price of the book will enable it to reach a wider circle. Interest in anaesthesia in Germany is certain to be still further stimulated by this little primer.

W. W. Mushin

Printed in Great Britain by JOHN SHERRATT & SON, Park Road, Altrincham

similarly

ced film
general
lowever,
instruc-

olmer

---

shed by
p. viii +

concise
of anaes-
ssistants
de them
nfamiliar
spicuous
by their
ook will
n anaes-
further

Iushin